

Renal anatomy

The tables below show the anatomical relations of the kidneys:

Right kidney

Direct contact	Layer of peritoneum in-between
Right suprarenal gland Duodenum Colon	Liver Distal part of small intestine

Left kidney

Direct contact	Layer of peritoneum in-between
Left suprarenal gland Pancreas Colon	Stomach Spleen Distal part of small intestine

Renal physiology

- Renal blood flow is 20-25% of cardiac output
- Renal cortical blood flow > medullary blood flow so, tubular cells more prone to ischaemia

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Proteinuria

- Proteinuria is an important marker of chronic kidney disease, especially for diabetic nephropathy.
- NICE recommend using albumin: creatinine ratio in preference to protein: creatinine ratio (PCR) when identifying patients with proteinuria as it has greater sensitivity.
- For quantification and monitoring of proteinuria, PCR can be used as an alternative, although ACR is recommended in diabetics.
- Urine reagent strips are not recommended unless they express the result as an ACR

Approximate equivalent values

ACR (mg/mmol)	PCR (mg/mmol)	Urinary protein excretion (g/24 h)
30	50	0.5
70	100	1

Collecting an ACR sample:

- by collecting a 'spot' sample it avoids the need to collect urine over a 24 hour period in order to detect or quantify proteinuria
- should be a first-pass morning urine specimen
- if the initial ACR is > 30 mg/mmol and < 70 mg/mmol, confirm by a subsequent early morning sample. If the initial ACR is > 70 mg/mmol a repeat sample need not be tested

Interpreting the ACR results:

- in non-diabetics an ACR > 30 mg/mmol is considered clinically significant proteinuria
- in diabetics microalbuminuria (ACR > 2.5 mg/mmol in men and ACR > 3.5 mg/mmol in women) is considered clinically significant

BP targets

- CKD with proteinuria ACR ≥ 70 mg/mmol or diabetes ---- blood pressure target < 130/80 mmHg.
- The NICE guidelines recommend that a blood pressure target < 140/90 mmHg should be used in non-diabetic patients with CKD and an ACR < 70 mg/mmol.
- NOT for lower systolic (<120 mmHg) or diastolic (<60 mmHg)

Haematuria

- The management of patients with haematuria is often difficult due to the absence of widely followed guidelines.
- It is sometimes unclear whether patients are best managed in primary care, by urologists or by nephrologists.
- The terminology surrounding haematuria is changing.
- Microscopic or dipstick positive haematuria is increasingly termed non-visible haematuria
- whilst macroscopic haematuria is termed visible haematuria
- Non-visible haematuria is found in around 2.5% of the population.

Causes of transient or spurious non-visible haematuria

- UTI
- menstruation
- sexual intercourse
- vigorous exercise (this normally settles after around 3 days)

Spurious causes - red/orange urine, where blood is not present on dipstick

- foods: beetroot, rhubarb
- drugs: rifampicin, doxorubicin, Metronidazole

Causes of persistent non-visible haematuria

- 1) cancer (bladder, renal, prostate)
- 2) stones
- 3) benign prostatic hyperplasia
- 4) prostatitis
- 5) urethritis e.g. *Chlamydia*
- 6) renal causes: IgA nephropathy, thin basement membrane disease

Management:

- ☒ Current evidence does not support screening for haematuria.
- ☒ The incidence of non-visible haematuria is similar in patients taking aspirin/warfarin to the general population hence these patients should also be investigated.

Testing

- 1) urine dipstick is the test of choice for detecting haematuria
 - ⇒ persistent non-visible haematuria is often defined as blood being present in **2 out of 3 samples** tested 2-3 weeks apart
- 2) BP, RFTs, and albumin:creatinine (ACR) or protein:creatinine ratio (PCR) should also be checked
- 3) urine microscopy may be used but time to analysis significantly affects the number of RBCs detected

NICE urgent cancer referral guidelines

- 1) of any age with **painless macroscopic** haematuria
- 2) patients under the age of 40 years with normal renal function, no proteinuria and who are normotensive do not need to be referred and may be managed in primary care
- 3) aged 40 years and older who present with **recurrent or persistent UTI** associated with **haematuria**
- 4) aged 50 years and older who are found to have **unexplained microscopic** haematuria

Acute kidney injury

Acute tubular necrosis vs. prerenal uraemia

Prerenal uraemia - kidneys hold on to sodium to preserve volume

	Pre-renal uraemia	Acute tubular necrosis
Urine sodium	< 20 mmol/L	> 30 mmol/L
Fractional sodium excretion*	< 1%	> 1%
Fractional urea excretion**	< 35%	>35%
Urine:plasma osmolality	> 1.5	< 1.1
Urine:plasma urea	> 10:1	< 8:1
Specific gravity	> 1020	< 1010
Urine	'bland' sediment	brown granular casts
Response to fluid challenge	Yes	No

*fractional sodium excretion = (urine sodium/plasma sodium) / (urine creatinine/plasma creatinine) x 100

**fractional urea excretion = (urine urea /blood urea) / (urine creatinine/plasma creatinine) x 100

Some notes from onexamination

- In acute tubular necrosis (ATN), urine to plasma osmolality should be less than 1.1, urinary sodium excretion is typically more than 60 mmol/L and urinary urea excretion less than 160 mmol/L.
- If this patient had a physiological oliguria, there would still be preservation of urine concentration, with low urinary sodium.
- Both ATN and pre-renal failure can present with a fall in urine output. There is such a marked variation in urine urea concentration, that it is seldom used as a clinical guide.

Non-steroidal anti-inflammatory drugs (NSAIDs) may cause:

- A reversible reduction in the glomerular filtration rate
- Acute tubular necrosis
- Acute interstitial nephritis often with heavy proteinuria
- Renal papillary necrosis, and
- Chronic tubulointerstitial nephritis.

NSAIDs may reduce glomerular perfusion by inhibiting production of prostaglandins which dilate the afferent arteriole of the glomerulus. The reduction in blood supply to the kidney results in impairment of kidney function.

As a rule, one should be cautious about prolonged prescription of NSAIDs in the elderly, or in those with existing renal impairment.

Acute interstitial nephritis

- Acute interstitial nephritis is inflammation of the renal tubulo-interstitium, secondary to a hypersensitivity reaction to drugs.
- Characterized by interstitial inflammation and edema.
- Left untreated this results in interstitial fibrosis.
- A definitive diagnosis is established by renal biopsy, although eosinophiluria and gallium 67 scanning are also suggestive.
- 60-70% of cases of acute interstitial nephritis are induced by exposure to drugs.
- The mechanism is via a **delayed T-cell hypersensitivity** or **cytotoxic T-cell reaction**.
- This is not typically dose-dependent.
- Multiple medications have been implicated, and the presentation and laboratory findings vary according to the class of drug involved.
- The most common drug related cause is NSAIDs.

Agents which are commonly implicated:

- NSAIDS
- Penicillins, (especially methicillin)
- Cephalosporins
- Rifampicin
- Sulphonamides
- Amphotericin
- Cimetidine
- Diuretics (thiazides, furosemide)
- Antivirals (aciclovir, foscarnet)
- Allopurinol, and
- Cyclosporin.

Features:

- Features include acute, most commonly oliguric renal failure, with or without systemic features which include fever, arthralgia and skin rashes.
 - Many patients have eosinophilia, raised serum IgE and eosinophiluria.
- Classic presenting features include **fever**, **maculopapular rash** and **arthralgia**. **Mild eosinophilia** is common, and **eosinophiuria** is **pathognomonic**.

Diagnosis

- **Renal biopsy** shows oedema of the interstitium with infiltration of plasma cells, lymphocytes and eosinophils, with acute tubular necrosis and variable tubular dilatation.

Management:

- Cessation of the causative agent
- Corticosteroids can have a beneficial effect, especially if initiated early.
- The treatment may involve dialysis until normal renal function returns.

Prognosis:

- In general, the prognosis of drug-induced acute interstitial nephritis is good, and partial or complete recovery of renal function is normally seen.

Papillary necrosis

Causes

- chronic analgesia use
- sickle cell disease
- TB
- acute pyelonephritis
- diabetes mellitus

Features

- fever, loin pain, haematuria
- IVU - papillary necrosis with renal scarring - 'cup & spill'

Nephrotoxicity due to contrast media

Contrast media nephrotoxicity may be defined as a 25% increase in creatinine occurring within 3 days of the intravascular administration of contrast media.

Risk factors include

- known renal impairment (especially diabetic nephropathy)
- age > 70 years
- dehydration
- cardiac failure
- the use of nephrotoxic drugs such as NSAIDs

Prevention

- the evidence base currently supports the use of intravenous 0.9% NaCl at a rate of 1 mL/kg/hour for 12 hours pre- and post- procedure. There is also evidence to support the use of isotonic sodium bicarbonate
- N-acetylcysteine (usually given orally) has been shown to reduce the incidence of contrast-nephropathy in some studies but the evidence base is not as strong as for fluid therapy

Rhabdomyolysis

Rhabdomyolysis will typically feature in the exam as a patient who has had a fall or prolonged epileptic seizure and is found to have acute renal failure on admission

Features:

- acute renal failure with disproportionately raised creatinine
- elevated CK
- myoglobinuria
- hypocalcaemia (myoglobin binds calcium)
- elevated phosphate (released from myocytes)

Causes:

- seizure
- collapse/coma (e.g. elderly patients collapses at home, found 8 hours later)
- ecstasy (MDMA)
- crush injury
- McArdle's syndrome
- drugs: statins

Management

- IV fluids to maintain good urine output
- urinary alkalinization is sometimes used

Early fluid resuscitation is the most important measure in the prevention of acute kidney injury secondary to rhabdomyolysis. Large volume depletion occurs due to sequestration of water by injured muscle. Volumes of up to 10 litres in 24 hours may be required. Most studies target urine outputs of 3 ml per kilogram per hour or >300 ml per hour.

Acute vs. chronic renal failure

Best way to differentiate is renal ultrasound, most patients with CRF have bilateral small kidneys

Exceptions

- autosomal dominant polycystic kidney disease ADPKC
- diabetic nephropathy
- amyloidosis
- HIV-associated nephropathy

Other features suggesting CRF rather than ARF

hypocalcaemia (due to lack of vitamin D)

Chronic kidney disease causes

Common causes of chronic kidney disease

- diabetic nephropathy
- chronic glomerulonephritis
- chronic pyelonephritis
- hypertension
- adult polycystic kidney disease

eGFR and classification

- Serum creatinine may not provide an accurate estimate of renal function due to differences in muscle. For this reason formulas were developed to help estimate the glomerular filtration rate (estimated GFR or eGFR).
- The most commonly used formula is the Modification of Diet in Renal Disease (MDRD) equation, which uses the following variables:
 - serum creatinine
 - age
 - gender
 - ethnicity

Factors which may affect the result

- pregnancy
- muscle mass (e.g. amputees, body-builders)
- eating red meat 12 hours prior to the sample being taken

CKD may be classified according to GFR:

CKD stage	GFR range
1	> 90 ml/min, with some sign of kidney damage on other tests (if all the kidney tests* are normal, there is no CKD)
2	60-90 ml/min with some sign of kidney damage (if kidney tests* are normal, there is no CKD)
3a	45-59 ml/min, a moderate reduction in kidney function
3b	30-44 ml/min, a moderate reduction in kidney function
4	15-29 ml/min, a severe reduction in kidney function
5	< 15 ml/min, established kidney failure - dialysis or a kidney transplant may be needed

*i.e. normal U&Es and no proteinuria

The National Institute for Health and Care Excellence guidelines on the identification and management of chronic kidney disease recommend that; screening for chronic kidney disease should be offered to patients with:

- Diabetes
- Hypertension
- Cardiovascular disease
- Structural renal tract pathology
- Multisystem disease with potential renal involvement
- Opportunistically detected haematuria or proteinuria
- A family history of stage 5 chronic kidney disease, or
- Hereditary kidney disease.

In the absence of other risk factors the guidelines recommend that age, gender and ethnicity should not be used as risk markers to test people for chronic kidney disease. Obesity alone should not be used as a risk factor (features of the metabolic syndrome should also be present).

Anaemia in Chronic kidney disease

- Patients with chronic kidney disease (CKD) may develop anaemia due to a variety of factors, the most significant of which is reduced erythropoietin levels. This is usually a normochromic normocytic anaemia and becomes apparent when the GFR is less than 35 ml/min (other causes of anaemia should be considered if the GFR is > 60 ml/min).
- Anaemia in CKD predisposes to the development of LVH - associated with a threefold increase in mortality in renal patients

Causes of anaemia in renal failure:

- reduced erythropoietin levels - the most significant factor
- reduced erythropoiesis due to toxic effects of uraemia on bone marrow
- reduced absorption of iron
- anorexia/nausea due to uraemia
- reduced red cell survival (especially in haemodialysis)
- blood loss due to capillary fragility and poor platelet function
- stress ulceration leading to chronic blood loss

Management:

- the 2011 NICE guidelines suggest a target haemoglobin of 10 - 12 g/dl
- determination and optimisation of iron status should be carried out prior to the administration of erythropoiesis-stimulating agents (ESA)
- Many patients, especially those on haemodialysis, will require IV iron
- ESAs such as erythropoietin and darbepoetin should be used in those 'who are likely to benefit in terms of quality of life and physical function'

Erythropoietin

- Erythropoietin is a haematopoietic growth factor that stimulates the production of erythrocytes.
- The main uses of erythropoietin are to treat the anaemia associated with CKD and that associated with cytotoxic therapy.

Side-effects of erythropoietin

- accelerated hypertension potentially leading to encephalopathy and seizures (blood pressure increases in 25% of patients)
- bone aches
- flu-like symptoms
- skin rashes, urticaria (pruritus of Hyperviscosity Syndrome)
- pure red cell aplasia (due to antibodies against erythropoietin)
The risk is greatly reduced with darbepoetin (Aranesp)
- raised PCV increases risk of thrombosis (e.g. Fistula)
- iron deficiency 2nd to increased erythropoiesis

Why patients may fail to respond to erythropoietin therapy:

- iron deficiency
 - inadequate dose
 - concurrent infection/inflammation (MIA)
 - hyperparathyroid bone disease
 - aluminium toxicity
-
- Due to the mild chronic inflammatory nature of chronic renal disease a ferritin <100 µg/L should be considered an indicator of absolute iron deficiency.
 - **Transferrin saturation** <20% should be considered a marker of functional iron deficiency when the ferritin is >100 µg/L.
 - Transferrin saturation - Circulating transferrin normally is about one-third saturated with iron (i.e., Fe/TIBC = 1/3, when both are expressed as micrograms of iron per 100 mL of plasma).

Conditions in which transferrin saturation is reduced (expressed as a percentage) include those in which the supply of iron to the plasma from the macrophage and other storage sites is reduced. These include:

- Iron deficiency anemia
- The anemia of chronic disease (anemia of chronic inflammation), and
- Some patients with a ferroportin mutation

Transferrin saturation is increased (expressed as a percentage) in those conditions in which the supply of iron is excessive or is greater than the current demand. These include:

- Most cases of hereditary and acquired hemochromatosis
- Aplastic anemia,
- bone marrow suppression
- Sideroblastic anemias
- Ineffective erythropoiesis
- Liver disease with reduced transferrin synthesis, and
- Monoclonal immunoglobulin with antitransferrin activity (rare).

☒ It is recommended that patients with anaemia secondary to chronic renal failure should have:

- a ferritin level maintained at 200-500 µg/L and either
 - transferrin saturations >20% or
 - percentage hypochromic red cells <6%
-
- Where patients have **absolute iron deficiency** oral iron supplementation may be adequate. However where there is **functional iron deficiency**, intravenous iron replacement is recommended.
-
- Erythropoietin should be commenced when anaemia has reached a level requiring treatment and usually only after the patient has had their iron stores adequately replaced.
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- Blood transfusion may be indicated where there are severe symptoms of anaemia or a particularly low haemoglobin level.
 - Where possible blood transfusion should be avoided in patients who may be candidates for transplantation as the development of antibodies to alloantigens may make future transplantation more problematic.

Life-threatening hyperkalaemia with changes on the ECG:

- The first step in treatment must be to administer **calcium gluconate** in order to stabilise the myocardium. However remember that definitive treatment to reduce the potassium level needs to be initiated soon after.
- **Calcium resonium** is an ion exchange resin which, when taken orally, prevents potassium from being absorbed in the diet. It acts to deplete the body of potassium (by preventing absorption) and takes **at least 24-48 hours** to have an effect. It is not suitable as an emergency treatment.
- The definitive treatment for this patient's hyperkalaemia and acidosis will be **haemodialysis** however this may take a little time to instigate and in the meantime treatment must be instituted in order to stabilise the myocardium. Holding measures such as insulin/dextrose infusions may not be necessary if dialysis can be organised rapidly.
- **Nebulised salbutamol** may be effective in lowering the serum potassium concentration however it should be noted that up to 40% of patients who are dependent upon dialysis do not demonstrate a fall in serum potassium in response to nebulised salbutamol.
- metabolic acidosis contribute to the hyperkalaemia (potassium moves out of cells as hydrogen ions are moved into cells in order to buffer the extracellular pH).
- Despite this sodium bicarbonate is not generally recommended for the treatment of acute hyperkalaemia as it may fail to lower the serum potassium, can take up to 60 minutes to work and is associated with potential sodium and volume overload.

Primary hyperparathyroidism is associated with hypercalcaemia and an inappropriately raised parathyroid hormone, the phosphate level is typically low.

Secondary hyperparathyroidism is associated with hypocalcaemia and an appropriately elevated parathyroid hormone level, the phosphate level is variable depending upon the aetiology (high in renal failure, low in vitamin D deficiency).

Hypercalcaemia of malignancy and iatrogenic hypercalcaemia would both be associated with a high calcium and **low parathyroid hormone level**.

Secondary hyperparathyroidism and hyperphosphataemia as a result of chronic renal failure:

- **Calcium containing phosphate binder** such as calcium acetate would be an appropriate first treatment to try. In conjunction with dietary phosphate restriction this will help reduce the plasma phosphate and the additional calcium may well be sufficient to increase the plasma calcium enough to bring it into the normal range.
- **Alfacalcidol** is 1 μ -hydroxylated vitamin D and is used when vitamin D supplementation is required in chronic renal failure in order to maintain the calcium within the normal range and control the levels of parathyroid hormone.
- A slightly elevated parathyroid hormone level is actually desirable in the management of renal bone disease. Suppression is not generally necessary until levels exceed 300 ng/L.
- **Sevelamer** is phosphate binders - whilst they would help correct the elevated phosphate they would not have any impact on the low calcium.
- **Adcal-D3** is not recommended for use in chronic renal disease as the vitamin D it contains is non-activated and the presence of renal failure means that it cannot be activated in the kidney. The calcium carbonate it contains could act as a phosphate binder if taken in the appropriate manner (with meals).
- Dairy products are high in phosphate content. cheddar cheese contain very high phosphate.
- Phosphate level is important to control in patients with chronic renal failure.
- Although high phosphate can cause symptoms such as itching, there are long term adverse cardiovascular effects.
- Foods that are characteristically rich in phosphate include dairy products, fibre rich foods, chocolate, and processed meats.

In chronic kidney disease due to deficiency of activated vitamin D patients may develop tertiary hyperparathyroidism;

- Biochemically this is characterised by raised calcium, raised (or sometimes normal) phosphate and grossly elevated parathyroid hormone levels. The most appropriate treatment once this has developed is **parathyroidectomy**.
- **Cinacalcet** is a **calcimimetic agent** which mimics the effect of calcium on the parathyroid gland. It is effective in controlling excess parathyroid hormone production and reducing calcium levels in tertiary hyperparathyroidism however it is currently recommended only in patients who are not fit for surgical parathyroidectomy.
- **Lanthanum** and **sevelamer** are both **non-calcium containing phosphate binders** which may be used, in conjunction with diet, to control high phosphate levels seen in chronic renal failure.
- **Bisphosphonates** such as pamidronate do not have a role in the management of hypercalcaemia in renal bone disease.

Hypertension in Chronic kidney disease

- The majority of patients with chronic kidney disease (CKD) will require more than two drugs to treat hypertension.
- ACE inhibitors are first line and are particularly helpful in proteinuric renal disease (e.g. diabetic nephropathy). As these drugs tend to reduce filtration pressure a small fall in glomerular filtration pressure (GFR) and rise in creatinine can be expected. NICE suggest that a decrease in eGFR of up to 25% or a rise in creatinine of up to 30% is acceptable, although any rise should prompt careful monitoring and exclusion of other causes (e.g. NSAIDs). A rise greater than this may indicate underlying renovascular disease
- Furosemide is useful as a anti-hypertensive in patients with CKD, particularly when the GFR falls to below 45 ml/min*. It has the added benefit of lowering serum potassium. High doses are usually required. If the patient becomes at risk of dehydration (e.g. Gastroenteritis) then consideration should be given to temporarily stopping the drug

*the NKF K/DOQI guidelines suggest a lower cut-off of less than 30 ml/min

- The NICE guidelines on the management of [Chronic kidney disease \(CG182\)](#) recommend that patients with chronic kidney disease who have proteinuria equivalent to ACR ≥ 70 mg/mmol should have their blood pressure controlled to the target range 120-129/<80 mmHg. The same target range should be used in patients with diabetes.
- The NICE guidelines recommend that a blood pressure target range of 120-139/<90 mmHg should be used in non-diabetic patients with chronic kidney disease and an ACR <70 mg/mmol.
- Aiming for lower systolic (<120 mmHg) or diastolic (<60 mmHg) blood pressures increases the risk of mortality, cardiovascular disease, congestive cardiac failure and, in the case of low diastolic values, progression of chronic kidney disease.
- Systolic or diastolic blood pressures above the target ranges are associated with increased risk of a doubling in serum creatinine, end-stage renal failure and death.

Risk factors for the progression of chronic kidney disease

- Hypertension, diabetes and the presence of proteinuria are well-recognised and accepted risk factors for the progression of chronic kidney disease (CKD).
- Cardiovascular disease is also a known risk factor for progression in chronic renal impairment.
- In patients with chronic kidney disease these risk factors should be actively managed to slow any fall in glomerular filtration rate.
- Aspirin usage has been suggested as a possible risk factor for the progression of chronic kidney disease. However it is widely used in patients with cardiovascular disease, which in itself is a risk factor for progression of chronic kidney disease. This is a significant confounding factor in the evidence base investigating a link between the drug and progressive decline in glomerular filtration rate.
- The evidence that smoking and ethnicity (Afro-Caribbean and Asian ethnicity) are risk factors for CKD progression is suggestive but inconclusive.
- There is no significant evidence that obesity affects the progression in CKD.
- Short term non-steroidal anti-inflammatory drug use is associated with a reversible decline in glomerular filtration rate. Chronic use in patients with CKD may be associated with a progressive and irreversible fall in glomerular filtration rate.

Diabetic nephropathy

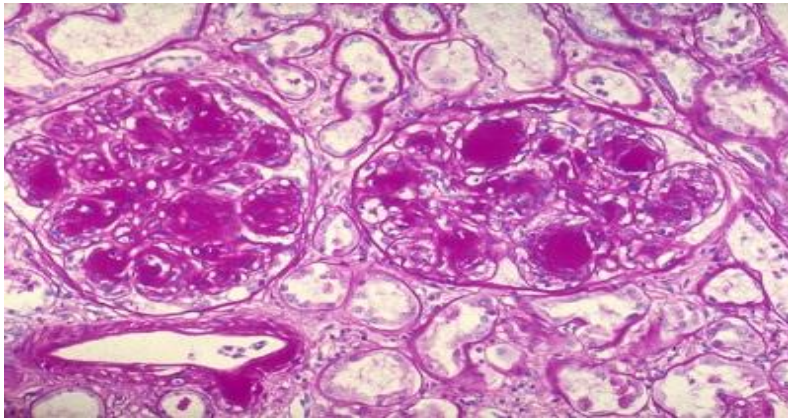
- commonest cause of end-stage renal disease (ESRD) in the western world
- 33% of patients with type 1 diabetes mellitus have diabetic nephropathy by the age of 40 years
- approximately 5-10% of patients with type 1 diabetes mellitus develop (ESRD)

The pathophysiology is poorly understood, however:

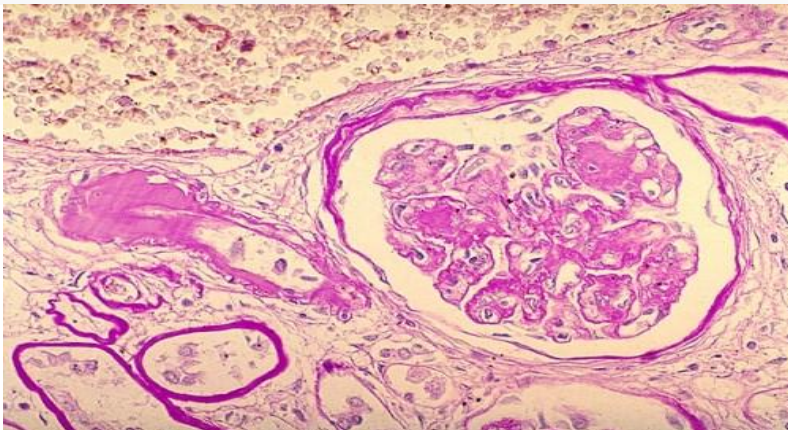
- changes to the haemodynamics of the glomerulus is thought to be key, which leads to an increased glomerular capillary pressure

Histological changes include:

- ⇒ BM thickening,
- ⇒ capillary obliteration,
- ⇒ mesangial widening.
- ⇒ Nodular hyaline areas develop in the glomeruli - Kimmelstiel-Wilson nodules



Thickening of the basement membrane is seen alongside multiple Kimmelstiel-Wilson nodules



Severe arteriolosclerosis is seen in the afferent arteriole on the left of the slide. Multiple, smaller acellular nodules are seen in the glomerulus - Kimmelstiel-Wilson nodules.

The tubular basement membrane is also thickened

Risk factors for developing diabetic nephropathy

Modifiable	Non-modifiable
Hypertension Hyperlipidaemia Smoking Poor glycaemic control Raised dietary protein	Male sex Duration of diabetes Genetic predisposition (e.g. ACE gene polymorphisms)

Stages of Diabetic nephropathy:

Diabetic nephropathy may be classified as occurring in five stages*:

Stage 1

- hyperfiltration: increase in GFR
- may be reversible

Stage 2 (silent or latent phase)

- most patients do not develop microalbuminuria for 10 years
- GFR remains elevated

Stage 3 (incipient nephropathy)

- microalbuminuria (albumin excretion of 30-300 mg/day, dipstick negative)(ACR >2.5)

Stage 4 (overt nephropathy)

- persistent proteinuria (albumin excretion > 300 mg/day, dipstick positive)
- hypertension is present in most patients
- histology shows diffuse glomerulosclerosis and focal glomerulosclerosis (Kimmelstiel-Wilson nodules)

Stage 5

- ESRD, GFR typically < 10ml/min
- RRT needed

The timeline given here is for type 1 diabetics. Patients with type 2 diabetes mellitus (T2DM) progress through similar stages but in a different timescale - some T2DM patients may progress quickly to the later stages

- In the setting of diabetes and stable renal function the albumin:creatinine ratio is considered the most appropriate test to detect and quantify proteinuria.
- Ideally the test should be performed on an early morning sample.
- It is more sensitive than the protein:creatinine ratio for low levels of proteinuria and more reliable than a 24 hour urinary collection for protein.
- The albumin:creatinine ratio is the test of choice in patients with diabetes due to the need to detect and treat microalbuminuria.
- 24 hour urine collections for protein are fraught with difficulty. Despite often being referred to as the 'gold standard' for measuring proteinuria they are subject to inaccuracies due to incomplete collection of all urine voided or inaccurate timing, and the biochemical methods used to quantify the amount of protein present give different results.
- For low levels of proteinuria the PCR is less sensitive than ACR. Once significant proteinuria has been detected the PCR may be used for follow up.
- Urine dipsticks are not recommended as a method for accurately determining whether there is proteinuria as they cannot reliably detect low-level protein loss or quantify the amount.
- Urine protein electrophoresis may be used if there is a suspicion of a urinary paraprotein (that is, Bence Jones proteins).
- Microalbuminuria is defined as an ACR of 2.5-30 mg/mmol in men and 3.5-30 mg/mmol in women. This is roughly equivalent to the loss of 30-300 mg of albumin in the urine per 24 hours.
- In patients with diabetes, microalbuminuria is used as a therapeutic target that can be modified by renin-angiotensin-aldosterone system blockade with a resulting improvement in clinical outcomes.
- All patients with diabetes and microalbuminuria should be offered therapy with an ACE inhibitor or angiotensin receptor blocker irrespective of whether they have hypertension. The chosen drug should be started at an appropriate starting (low) dose and titrated upwards to the target dose as tolerated with monitoring of renal function.
- The predominant protein lost in urine is albumin and the albumin:creatinine ratio is a significantly more sensitive test for low level proteinuria than the protein:creatinine ratio.
- In patients with diabetes the albumin:creatinine ratio should always be used in order to determine whether or not there is clinically significant renal protein loss. Once established the protein:creatinine ratio may be used for follow-up measurements though the ACR is usually recommended in patients with diabetes.
- Where the initial result is borderline the albumin:creatinine ratio should be repeated on an early morning urine sample (a morning sample is best as the urine is most concentrated and thus the concentration of protein will be highest and more likely to be detected). This is recommended in non-diabetic patients with an initial ACR of 30-70 mg/mmol.

ARPKD

- Autosomal recessive polycystic kidney disease (ARPKD) is much less common than autosomal dominant disease (ADPKD).
 - It is due to a defect in a gene located on **chromosome 6**
-
- ☒ Diagnosis may be made on prenatal ultrasound or in early infancy with abdominal masses and renal failure.
 - ☒ Newborns may also have features consistent with **Potter's syndrome** secondary to **oligohydramnios**.
 - ☒ ESRD develops in childhood.
 - ☒ Patients also typically have liver involvement, for example portal and interlobular fibrosis.
 - ☒ Renal biopsy typically shows **multiple cylindrical lesions at right angles to cortical surface**.

Autosomal dominant polycystic kidney disease

(ADPKD)

- The most common inherited cause of kidney disease, affecting 1 in 1,000 Caucasians.
- Two disease loci have been identified, PKD1 and PKD2, which code for polycystin-1 and polycystin-2 respectively

ADPKD type 1	ADPKD type 2
85% of cases	15% of cases
Chromosome 16	Chromosome 4
Presents with renal failure earlier	

- The screening investigation for relatives is abdominal ultrasound (start at 18 years)
- Formal screening for AKPD occurs in early adulthood, usually with a renal ultrasound scan.
- Its sensitivity approaches 100% in those over 30 years, but falls to less than 70% under this age.

Ultrasound diagnostic criteria (in patients with positive family history)

- two cysts, unilateral or bilateral, if aged < 30 years
- two cysts in both kidneys if aged 30-59 years
- four cysts in both kidneys if aged > 60 years

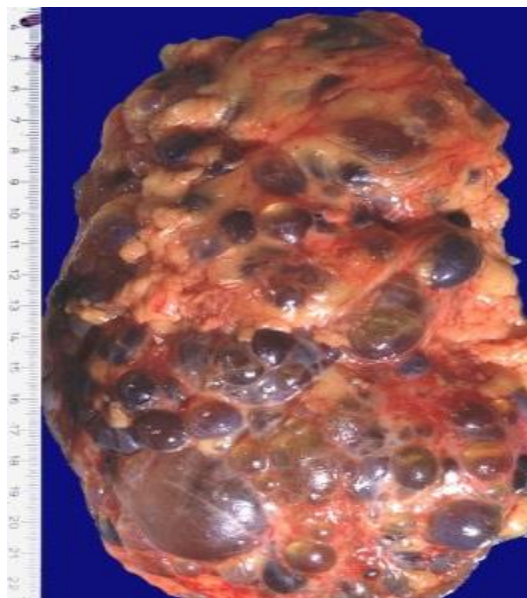
Features

- hypertension
- recurrent UTIs
- abdominal pain
- renal stones
- haematuria
- chronic kidney disease

Extra-renal manifestations

- Liver cysts (70%)
- Berry aneurysms (8%)
- cardiovascular system:
 - ☒ mitral valve prolapse,
 - ☒ mitral/tricuspid incompetence,
 - ☒ aortic root dilation, aortic dissection
- cysts in other organs: pancreas, spleen; very rarely: thyroid, oesophagus, ovary

- On average, patients progress to end stage renal failure between the ages of 40 and 60 years.
- In these patients the renal function usually deteriorates in a gradual fashion, usually with a drop in creatinine clearance of **5/6 ml/min/year** (at least 10 years for this patient or possibly sooner if BP not adequately managed).
- **Treatment should include** a **high fluid intake** (to prevent the formation of renal stones or blood clots) and regular follow up of blood pressure and renal function.
- **Loin pain** should be treated **symptomatically**, and
- **Hypertension** should be managed with **standard antihypertensive medications**.
- **Haematuria** should be treated **conservatively**.
- **Urinary tract infections** should be treated with **lipophilic drugs** (for example, **ciprofloxacin**, **trimethoprim-sulphamethoxazole**) as they have the best penetration into cyst fluid.
- It is an autosomal dominant disease, therefore the offspring of an affected patient has a 50% chance of inheriting the disease.
- The patient should be offered genetic counselling, despite the fact that the disease has a variable clinical course even between affected family members.



Extensive cysts are seen in an enlarged kidney



CT showing multiple cysts of varying sizes in the liver, and bilateral kidneys with little remaining normal renal parenchyma.

Magnetic resonance angiography is usually only recommended in patients with a diagnosis of polycystic kidney disease who have;

- 1) symptoms of an intracranial aneurysm (ICA),
- 2) a previous ICA,
- 3) a high-risk job should intracranial haemorrhage occur or
- 4) An affected family member with an ICA.

Alport's syndrome

- Usually inherited in an **X-linked dominant** pattern*.
- It is due to a defect in the gene which codes for type IV collagen resulting in an abnormal glomerular-basement membrane (GBM).
- The disease is more severe in males
- females **rarely** developing renal failure
- Patients with Alport syndrome are at risk of developing antiglomerular basement membrane disease (Goodpasture's disease) following transplantation, as their immune systems have never been exposed to type IV collagen and hence lack tolerance.
- **Favourite question is an Alport's patient with a failing renal transplant. This may be caused by presence of anti-GBM antibodies leading to Goodpasture's syndrome like picture**
- Alport's syndrome usually presents in childhood.
- Type IV collagen is found in the basement membrane of the kidney, inner ear and eye, so therefore extra-renal manifestations include bilateral sensorineural deafness and ocular abnormalities such as corneal dystrophies and lens abnormalities.

The following features may be seen:

- microscopic and macroscopic haematuria with or without proteinuria
 - progressive renal failure
 - bilateral sensorineural deafness
 - lenticonus: protrusion of the lens surface into the anterior chamber
 - retinitis pigmentosa
 - renal biopsy: splitting of lamina densa seen on EM
-
- ☒ The disease is **X-linked dominant** in 85% of cases
 - ☒ 10-15% of cases are inherited in an autosomal recessive fashion with rare autosomal dominant variants existing
 - ☒ the most common genetic abnormality is a mutation in the COL4A5 gene (involved in type IV collagen synthesis) on the X chromosome
 - ☒ COL4A3 and COL4A4 (genes also involved in type IV collagen synthesis) are located on chromosome 2, explaining why this disease may also have autosomal recessive or dominant inheritance.
 - ☒ As Alport syndrome is X linked in 85% of cases. Therefore, as only the Y chromosome is passed from father to son there is no chance of the son having the disease from only affected father

Goodpasture's syndrome

- Goodpasture's syndrome is rare condition
- Associated with:
 - ⇒ Pulmonary haemorrhage and
 - ⇒ Rapidly progressive glomerulonephritis.
- It is caused by **anti-glomerular basement membrane** (anti-GBM) antibodies against type **IV collagen**.
- Goodpasture's syndrome is more common in **men** (sex ratio 2:1)
- It has a **bimodal age** distribution (peaks in 20-30 and 60-70 age bracket).
- It is associated with **HLA DR2**.

Features:

- 1) pulmonary haemorrhage
- 2) followed by **RPGN** rapidly progressive glomerulonephritis

Factors which increase likelihood of pulmonary haemorrhage:

- 1) young males
- 2) smoking
- 3) inhalation of hydrocarbons
- 4) lower respiratory tract infection
- 5) pulmonary oedema

Investigations:

- 1) renal biopsy: **linear IgG deposits** along BM
- 2) **raised transfer factor** secondary to pulmonary haemorrhages

Management:

- 1) plasma exchange
- 2) steroids
- 3) cyclophosphamide

Nephritic syndrome

Nephritic syndrome consists of:

- Oliguria
- Acute renal failure
- Haematuria
- Hypertension
- Proteinuria
- Oedema

☒ Outcome and treatment of nephritic syndrome depends on renal biopsy.

☒ Post-infectious glomerulonephritis is a diffuse proliferative glomerulonephritis with proliferation of capillaries, obliteration of capillary loops and 'wire-loop' lesions on light microscopy. There is antibody and complement deposition on immunostaining.

☒ A wire-loop lesion is a capillary loop with immune complex deposition circumferential around the loop. They may also be seen in lupus nephritis.

☒ Crescentic glomerulonephritis occurs in IgA nephropathy, small vessel vasculitis, Goodpasture's disease and systemic lupus erythematosus (SLE). It is less common in post-infectious glomerulonephritis.

SLE renal complications

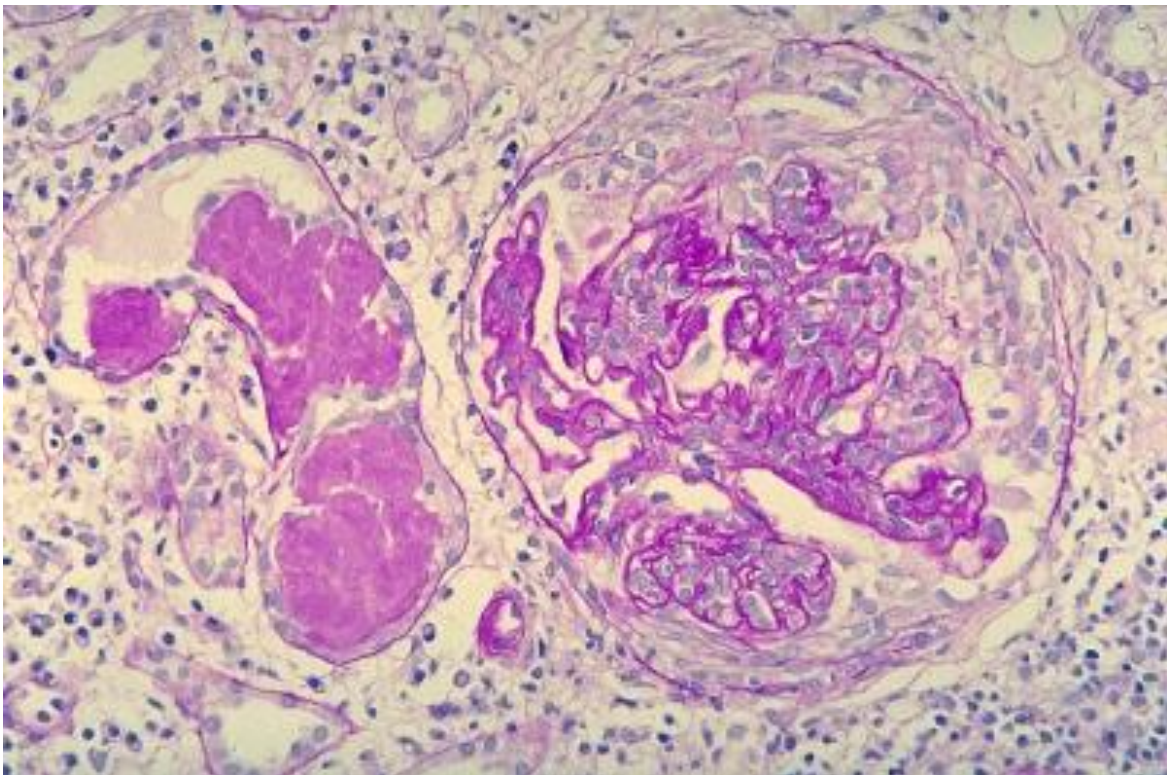
WHO classification

- **class I:** normal kidney
- **class II:** mesangial glomerulonephritis
- **class III:** focal (and segmental) proliferative glomerulonephritis
- **class IV:** diffuse proliferative glomerulonephritis
- **class V:** diffuse membranous glomerulonephritis
- **class VI:** sclerosing glomerulonephritis

Class IV (diffuse proliferative glomerulonephritis) is the most common and severe form.

Renal biopsy characteristically shows the following findings:

- glomeruli shows endothelial and mesangial proliferation, 'wire-loop' appearance
- if severe, the capillary wall may be thickened secondary to immune complex deposition
- electron microscopy shows subendothelial immune complex deposits
- granular appearance on immunofluorescence



Diffuse proliferative SLE. Proliferation of endothelial and mesangial cells. The thickening of the capillary wall results in a 'wire-loop' appearance. Some crescents are present.

Management

- treat hypertension
- corticosteroids if clinical evidence of disease
- immunosuppressants e.g. azathiopine/cyclophosphamide

Lupus nephritis

- Histologically, a number of different types of renal disease are recognised in SLE, with immune-complex mediated glomerular disease being the most common.
- The up to date International Society of Nephrology/Renal Pathology Society 2003 classification divides these into six different patterns:
 - ☒ I - minimal mesangial
 - ☒ II - mesangial proliferative
 - ☒ III - focal
 - ☒ IV - diffuse
 - ☒ V - membranous
 - ☒ VI - advanced sclerosis

I - minimal mesangial:

- Light microscopy ⇒ Glomeruli appear normal, but
- Immunofluorescence ⇒ demonstrates mesangial immune deposits.

II - Mesangial proliferative nephritis

- Presents clinically as microscopic haematuria and/or proteinuria.
- Hypertension is uncommon and nephrotic syndrome and renal impairment are very rarely seen.
- Biopsy demonstrates:
 - ⇒ Segmental areas of increased mesangial matrix and cellularity, with mesangial immune deposits.
 - ⇒ A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence.
- **The prognosis is good** and specific treatment is only indicated if the disease progresses.

III - Focal disease:

- More advanced, but still affects **< 50% of glomeruli**.
- Haematuria and proteinuria is almost always seen
- nephrotic syndrome, hypertension and elevated creatinine may be present.
- Biopsy demonstrates:
 - ⇒ Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving **< 50% of glomeruli**,
 - ⇒ typically with **focal subendothelial immune deposits**,
 - ⇒ with or without mesangial alterations
- It is further subdivided:
 - ☒ A: Active lesions: focal proliferative lupus nephritis
 - ☒ A/C: Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
 - ☒ C: Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
- **Prognosis** is variable.

IV - Diffuse glomerulonephritis:

- **The most common** and **severe** form of lupus nephritis.
- Haematuria and proteinuria are almost always present, and
- nephrotic syndrome, hypertension and renal impairment common.
- Biopsies demonstrate
 - ⇒ Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving > 50% of all glomeruli,
 - ⇒ typically with **diffuse subendothelial immune deposits**,
 - ⇒ with or without mesangial alterations
- This class is divided into:
 - ⇒ **Diffuse segmental (IV-S)** when more than 50% of the involved glomeruli have segmental lesions, and
 - ⇒ **Diffuse global (IV-G)** when more than 50% of involved glomeruli have global lesions. (Segmental is defined as a glomerular lesions that involves less than half of the glomerular tuft)
- ☒ IV-S (A): Active lesions, diffuse segmental proliferative lupus nephritis
- ☒ IV-G (A): Active lesions, diffuse global proliferative
- ☒ IV-S (A/C): Active and chronic lesions, diffuse segmental proliferative and sclerosing lupus nephritis
- ☒ IV-S (C): Chronic inactive lesions with scars, diffuse segmental sclerosing lupus nephritis
- ☒ IV-G (C): Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
- **Immunosuppressive therapy** is required in these cases to prevent progressive to end-stage renal failure.

V - Membranous lupus nephritis:

- Patients with membranous lupus nephritis tend to present with nephrotic syndrome.
- Microscopic haematuria and hypertension may also be seen.
- Biopsies show
 - ⇒ Global or segmental **subepithelial immune deposits** or their morphologic sequelae,
 - ⇒ with or without mesangial alterations
- It may occur in combination with class III or IV, in which case both are diagnosed.
- Progression is variable, and immunosuppression is not always needed.

VI - advanced sclerosis: >90% of glomeruli are globally sclerosed without residual activity.

- ☒ With regard to the management of lupus nephritis a biopsy is indicated in those patients with abnormal urinalysis and/or reduced renal function.
- ☒ This can provide a histological classification as well as information regarding activity, chronicity and prognosis.
- ☒ **Cyclophosphamide**, **mycophenolate mofetil** and **azathioprine** reduce mortality in proliferative forms of lupus glomerulonephritis.

Glomerulonephritides

Knowing a few key facts is the best way to approach the difficult subject of glomerulonephritis:

Minimal change disease

- Typically a child with nephrotic syndrome (accounts for 80%)
- causes: Hodgkin's, NSAIDs
- good response to steroids

Membranous glomerulonephritis

- presentation: proteinuria / nephrotic syndrome / chronic kidney disease
- cause: infections, rheumatoid drugs, malignancy
- 1/3 resolve, 1/3 respond to cytotoxics, 1/3 develop chronic kidney disease

Focal segmental glomerulosclerosis

- may be idiopathic or secondary to HIV, heroin
- presentation: proteinuria / nephrotic syndrome / chronic kidney disease

IgA nephropathy - aka Berger's disease, mesangioproliferative GN

- typically young adult with haematuria following an URTI

Diffuse proliferative glomerulonephritis

- classical post-streptococcal glomerulonephritis in child
- presents as nephritic syndrome / acute kidney injury
- most common form of renal disease in SLE

Rapidly progressive glomerulonephritis - aka crescentic glomerulonephritis

- rapid onset, often presenting as acute kidney injury
- causes include Goodpasture's, ANCA positive vasculitis

Mesangiocapillary glomerulonephritis (membranoproliferative)

- type 1: cryoglobulinaemia, hepatitis C
- type 2: partial lipodystrophy

Glomerulonephritis and low complement

- 1) Post-streptococcal glomerulonephritis
- 2) Subacute bacterial endocarditis
- 3) Systemic lupus erythematosus
- 4) Mesangiocapillary glomerulonephritis

Nephrotic syndrome

☒ Triad of:

- 1) **Proteinuria** (> 3g/24hr) causing
- 2) **Hypoalbuminaemia** (< 30g/L) and
- 3) **Oedema**

☒ Loss of antithrombin-III, proteins C and S and an associated rise in fibrinogen levels predispose to thrombosis.

☒ Loss of thyroxine-binding globulin lowers the total, but not free, thyroxine levels.

Nephrotic syndrome complications:

- increased risk of infection due to urinary immunoglobulin loss
- increased risk of thromboembolism related to loss of antithrombin III and plasminogen in the urine
- hyperlipidaemia
- hypocalcaemia (vitamin D and binding protein lost in urine)
- acute renal failure

Minimal change disease

- Always presents as nephrotic syndrome, accounting for 75% of cases in children and 25% in adults.
- The majority of cases are idiopathic, but in around 10-20% a cause is found:
 - 1) drugs: NSAIDs, rifampicin
 - 2) Hodgkin's lymphoma, thymoma
 - 3) infectious mononucleosis

Pathophysiology:

- T-cell and cytokine mediated damage to the GBM → polyanion loss
- the resultant reduction of electrostatic charge → increased glomerular permeability to serum albumin

Features:

- nephrotic syndrome
- normotension - hypertension is rare
- highly selective proteinuria: only intermediate-sized proteins such as albumin and transferrin leak through the glomerulus
- renal biopsy: electron microscopy shows fusion of podocytes

Management:

- majority of cases (80%) are steroid responsive
- cyclophosphamide is the next step for steroid resistant cases

Prognosis:

Prognosis is overall good, although relapse is common. Roughly:

- 1/3 have just one episode
- 1/3 have infrequent relapses
- 1/3 have frequent relapses which stop before adulthood

Membranous glomerulonephritis

- The commonest type of glomerulonephritis in adults
- The third most common cause of ESRF.
- It usually presents with nephrotic syndrome or proteinuria.

Renal biopsy demonstrates:

- EM: the basement membrane is thickened with subepithelial electron dense deposits. This creates a 'spike and dome' appearance

Causes:

- 1) idiopathic
- 2) infections: hepatitis B, malaria, syphilis
- 3) malignancy: lung cancer, lymphoma, leukaemia
- 4) drugs: gold, penicillamine, NSAIDs
- 5) autoimmune diseases: systemic lupus erythematosus (class V disease), thyroiditis, rheumatoid

Prognosis: rule of thirds

- one-third: spontaneous remission
- one-third: remain proteinuric (respond to cytotoxics)
- one-third: develop ESRF

Good prognostic features include:

- 1) female sex,
- 2) young age at presentation and
- 3) asymptomatic
- 4) proteinuria of a modest degree at the time of presentation

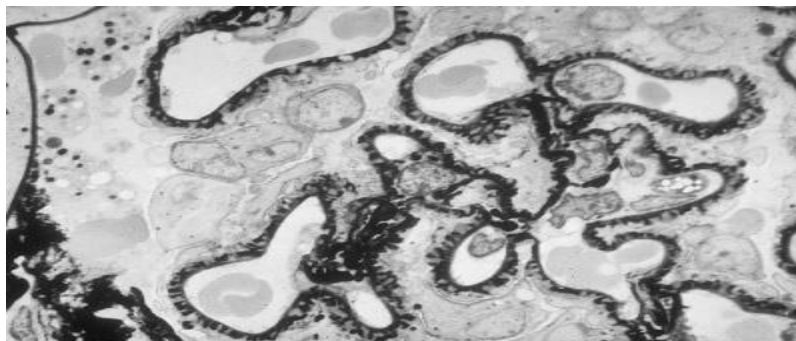
Management

1) **Immunosuppression:**

- ☒ A combination of corticosteroid + another agent such as chlorambucil is often used
- ☒ corticosteroids alone have **not** been shown to be **effective**

2) **blood pressure control:** ACE inhibitors have been shown to reduce proteinuria

3) **consider anticoagulation**



Silver-stained section showing thickened basement membrane, subepithelial spikes

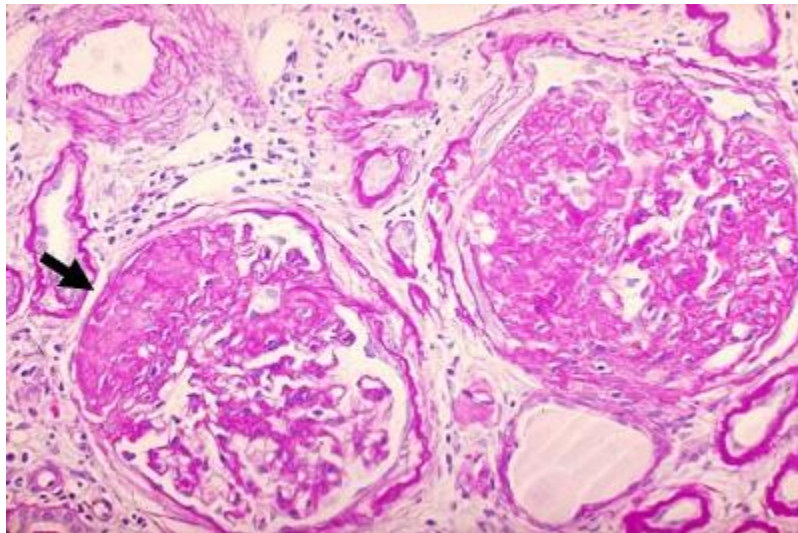
Focal segmental glomerulosclerosis

- A cause of nephrotic syndrome and chronic kidney disease.
- It generally presents in young adults.

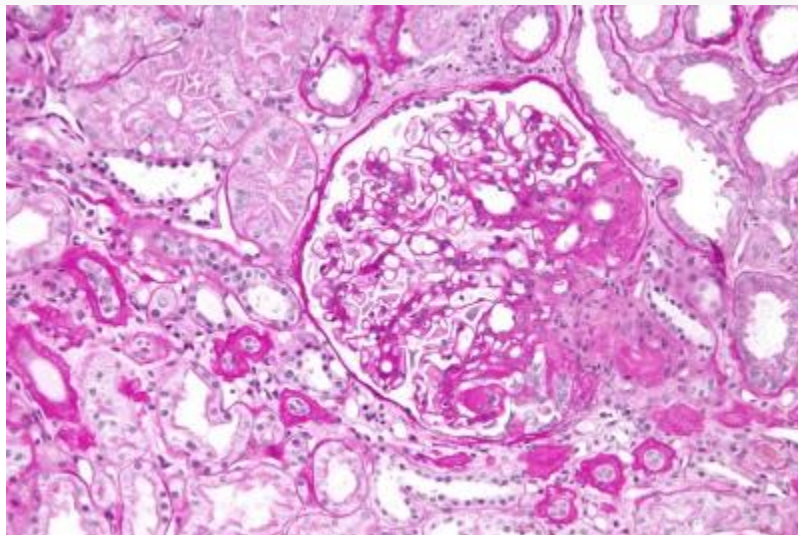
Causes:

- 1) idiopathic
- 2) secondary to other renal pathology e.g. IgA nephropathy, reflux nephropathy
- 3) HIV
- 4) heroin
- 5) Alport's syndrome
- 6) sickle-cell

- ☒ Focal segmental glomerulosclerosis is noted for having a high recurrence rate in renal transplants.



Sclerosis of the glomerulus is seen next to Bowman's capsule



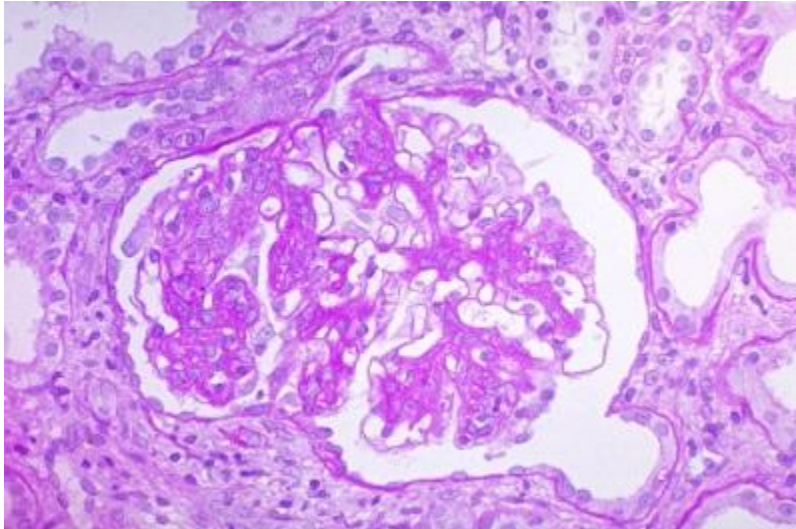
Sclerosis is seen in the perihilar region of the glomerulus

IgA nephropathy

- also called Berger's disease or mesangioproliferative glomerulonephritis
- commonest cause of glomerulonephritis worldwide
- thought to be caused by mesangial deposition of IgA immune complexes
- there is considerable pathological overlap with Henoch-Schonlein purpura (HSP)

Histology:

- ⇒ mesangial hypercellularity,
- ⇒ positive immunofluorescence for IgA & C3



Proliferation and hypercellularity of the mesangium is seen in the glomerulus

Presentations:

- young male, recurrent episodes of macroscopic haematuria
- typically associated with mucosal infections e.g., URTI
- nephrotic range proteinuria is rare
- renal failure

Associated conditions:

- alcoholic cirrhosis
- coeliac disease/dermatitis herpetiformis
- Henoch-Schonlein purpura

Management:

- steroids/immunosuppressants not be shown to be useful

Prognosis

- 25% of patients develop ESRF
- markers of good prognosis: frank haematuria
- markers of poor prognosis:
 - 1) male gender,
 - 2) proteinuria (especially > 2 g/day),
 - 3) hypertension, hyperlipidaemia
 - 4) smoking,
 - 5) ACE genotype DD

Differentiating between IgA nephropathy and post-streptococcal glomerulonephritis

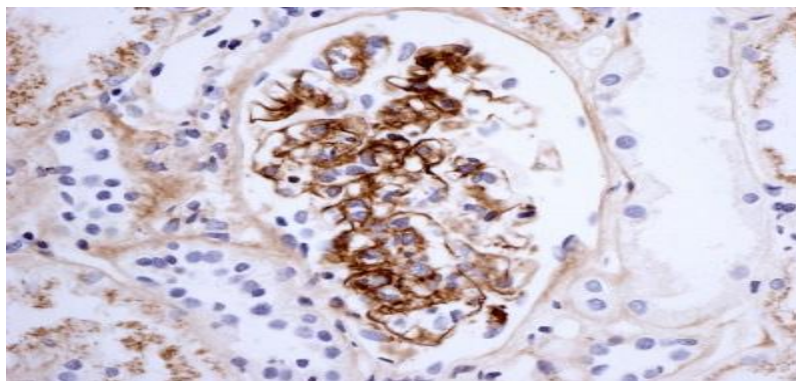
- 1) post-streptococcal glomerulonephritis is associated with low complement levels
- 2) main symptom in post-streptococcal glomerulonephritis is proteinuria (although haematuria can occur)
- 3) there is typically an interval between URTI and the onset of renal problems in post-streptococcal glomerulonephritis

Henoch-Schonlein purpura

- Henoch-Schonlein purpura (HSP) is an IgA mediated small vessel vasculitis.
- There is a degree of overlap with IgA nephropathy (Berger's disease).
- HSP is usually seen in children following an infection.

Features

- 1) palpable purpuric rash (with localized oedema) over buttocks and extensor surfaces of arms and legs (preceded by URTI group A streptococcal)
- 2) abdominal pain
- 3) polyarthrititis
- 4) features of IgA nephropathy may occur e.g. haematuria, renal failure



Immunostaining for IgA in a patient with HSP

Treatment:

- ☒ analgesia for arthralgia
- ☒ Treatment of nephropathy is generally supportive.
- ☒ There is inconsistent evidence for the use of steroids and immunosuppressants (used if severe or deteriorating disease)
- ☒ All patients with HTN and proteinuria (> 1 g/day-) should be started on (ACE) inhibitor,
- ☒ Once the BP has been controlled she should have a renal biopsy, and if this showed changes of **a crescentic glomerulonephritis (GN)**, then an immunosuppression regime similar to that used in renal vasculitis should be started (**high dose steroids +/- cyclophosphamide**).

Prognosis:

- usually excellent, HSP is a self-limiting condition, especially in children without renal involvement
- around 1/3rd of patients have a relapse

Membranoproliferative glomerulonephritis

- also known as mesangiocapillary glomerulonephritis
- may present as nephrotic syndrome, haematuria or proteinuria
- poor prognosis

Type 1:

- accounts for 90% of cases
- **subendothelial immune deposits** of electron dense material resulting in a '**tram-track**' appearance
- cause: **cryoglobulinaemia**, **hepatitis C**

Type 2: 'dense deposit disease' DDD

- causes: **partial lipodystrophy**, **factor H deficiency**
- **reduced serum complement**
- **C3b nephritic factor** (an antibody against C3bBb) found in 70%

Type 3

- causes: **hepatitis B** and **C**

Management

- steroids may be effective

Mesangiocapillary glomerulonephritis is treated with antiplatelet drugs, anticoagulants, corticosteroids and alkylating agents. Steroids are given for a prolonged period of time, and may have some benefit in some patients.

Minimal change glomerulonephritis is extremely steroid sensitive, with 80% of adult patients achieving remission within 16 weeks with prednisolone 60 mg per day.

Vasculitis

See rheumatology

Granulomatosis with polyangiitis

(Wegener's granulomatosis)

- Granulomatosis with polyangiitis is now the preferred term for Wegener's granulomatosis.
- an autoimmune condition associated with a **necrotizing granulomatous vasculitis**, affecting both the upper and lower **respiratory tract** as well as **the kidneys**

Features:

- 1) upper respiratory tract: epistaxis, sinusitis, nasal crusting
- 2) lower respiratory tract: dyspnoea, haemoptysis, cavitating lesions
- 3) rapidly progressive glomerulonephritis ('pauci-immune', 80% of patients)
- 4) **saddle-shape nose** deformity
- 5) also: vasculitic rash, eye involvement (e.g. **proptosis**), cranial nerve lesions

Investigations:

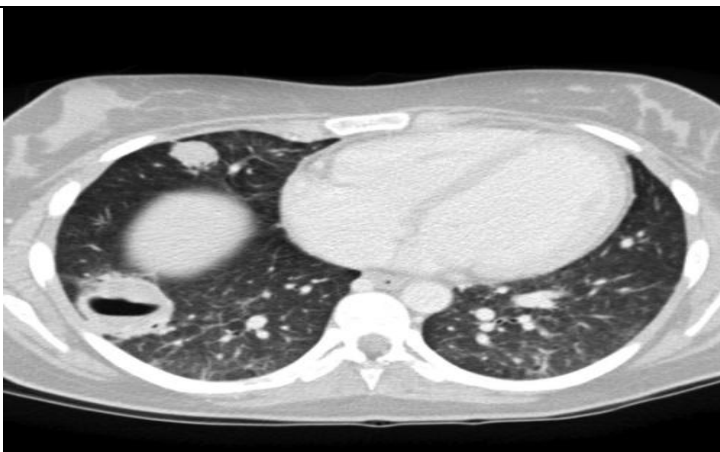
- 1) cANCA positive in > 90%, pANCA positive in 25%
- 2) chest x-ray: wide variety of presentations, including cavitating lesions
- 3) renal biopsy: **epithelial crescents** in Bowman's capsule

Management:

- 1) steroids
- 2) **cyclophosphamide (90% response)**
- 3) plasma exchange
- 4) median survival = 8-9 years



Chest x-ray from a young male patient with granulomatosis with polyangiitis. Whilst the changes are subtle it demonstrates a number of ill-defined nodules the largest of which projects over the dome of the right hemidiaphragm. This nodule appears to have a central lucency suggesting cavitation



CT of the same patient showing the changes in a much more obvious way, confirming the presence of at least 2 nodules, the larger of the two having a large central cavity and air-fluid level

- Usually the MPO antibody is associated with microscopic polyangiitis, whereas the PR3 antibody is associated with Wegener's granulomatosis, which is closely linked.

Haemolytic uraemic syndrome (HUS)

Haemolytic uraemic syndrome is generally seen in young children and produces a triad of:

- 1) acute renal failure
- 2) microangiopathic haemolytic anemia
- 3) thrombocytopenia

Causes:

- post-dysentery - classically E coli 0157:H7 ('verotoxigenic', 'enterohaemorrhagic')
- tumours
- pregnancy
- ciclosporin, the Pill
- SLE, HIV

Investigations:

- full blood count: anemia, thrombocytopaenia, fragmented blood film
- U&E: acute renal failure
- stool culture

Management:

- treatment is **supportive** e.g. Fluids, blood transfusion and dialysis if required
- there is **no role for antibiotics**, despite the preceding diarrhoeal illness in many patients
- The indications for plasma exchange in HUS are complicated. As a general rule **plasma exchange is reserved for severe cases of HUS not associated** with diarrhea

- ☒ HUS is a complication of infection with verocytotoxin producing *Escherichia coli* usually of the serotype 0157:H7.
- ☒ Toxins produced in the intestine enter the blood and bind to endothelial cells in target organs.
- ☒ Endothelial cell damage leads to platelet and fibrin deposition with resultant fragmentation of circulating red blood cells and microvascular occlusion.
- ☒ The syndrome has also been reported after infections with coxsackie, echovirus and *Shigella*.
- ☒ HUS is characterised by the sudden onset of haemolytic anaemia with fragmentation of red blood cells, thrombocytopenia and acute renal failure after a prodromal illness of acute gastroenteritis often with bloody diarrhoea.
- ☒ Clinical signs include increasing pallor, haematuria, oliguria and purpura. Jaundice is occasionally seen. Hypertension may be present.
- ☒ Typical results show an anaemia, thrombocytopenia, and often a neutrophilia. Blood film shows fragmented erythrocytes.
- ☒ **There is normal coagulation and fibrinogen.**
- ☒ Neurological complications include: Stroke, seizure and coma occur in 25% of patients
- ☒ Rarely pancreatitis, and Pleural and pericardial effusions.
- ☒ Approximately 5% of patients will develop end stage renal failure.
- ☒ Long term renal sequelae range from proteinuria to chronic renal failure.

☒ **Therapy is supportive with:**

- Correction of anaemia
- Correction of uraemia by early dialysis
- Strict fluid balance
- Treatment of hypertension.

Major differential diagnosis is:

- 1) Sepsis with DIC - presents with abnormalities of clotting parameters.
 - 2) TTP - thrombotic thrombocytopenic purpura presents with microangiopathic haemolytic anaemia, thrombocytopenic purpura, neurologic abnormalities, fever, and renal disease.
- ☒ Renal abnormalities tend to be more severe in HUS.
- ☒ Although once considered variants of a single syndrome, recent evidence suggests that the pathogenesis of TTP and HUS is different.
- ☒ Patients with TTP **lack a plasma protease** that is responsible for the breakdown of von Willebrand factor (vWF) multimers and these accumulate in the plasma. The activity of this protease is normal in patients with HUS.
- ☒ Until the test for vWF protease activity becomes available, differentiation between HUS and TTP is based on the presence of central nervous system involvement in TTP and the more severe renal involvement in HUS.
- ☒ In HUS 90% of patients are children and a history of prodromal diarrhoeal illness is more common.
- ☒ The therapy of choice for TTP is plasma exchange with fresh frozen plasma.

HIV: renal involvement

- Renal involvement in HIV patients may occur as a consequence of treatment or the virus itself.
- Protease inhibitors such as **indinavir** can precipitate **intratubular crystal obstruction**
- HIV-associated nephropathy (HIVAN) accounts for up to 10% of ESRD cases in the US.
- Antiretroviral therapy has been shown to alter the course of the disease.

There are five key features of HIVAN:

- 1) normal or large kidneys
 - 2) normotension
 - 3) massive proteinuria
 - 4) elevated urea and creatinine
 - 5) FSGS with focal or global **capillary collapse** on renal biopsy
- Patients also have raised immunoglobulins and raised cholesterol.
 - Prior to the availability of HAART (highly active anti-retroviral therapy), mean time to progression to end-stage renal failure was 2.5 months, however in the post-HAART era, the renal prognosis has significantly improved.
 - The pathogenesis of HIV associated nephropathy is unclear, and may be multi-modal involving direct effects of the HIV virus itself, the impact of cytokines, and differential expression of immune cells in patients who develop the disorder.

Cholesterol embolisation

- cholesterol emboli may break off causing renal disease
- seen more commonly in arteriopathies, abdominal aortic aneurysms

Features

- 1) eosinophilia
- 2) purpura
- 3) livedo reticularis
- 4) renal failure

Plasma exchange

Indications for plasma exchange

- Guillain-Barre syndrome
- myasthenia gravis
- TTP/HUS
- cryoglobulinaemia
- Goodpasture's syndrome
- ANCA positive vasculitis e.g. Wegener's, Churg-Strauss
- hyperviscosity syndrome e.g. secondary to myeloma, monoclonal gammopathy

In most conditions 5% albumin is the plasma substitute of choice , except for **TTP** where we use FFP as it has a therapeutic role in replacing the missing factor, ADAMTS-13.

Peritoneal dialysis

- Peritoneal dialysis (PD) is a form of renal replacement therapy.
- It is sometimes used as a stop-gap to haemodialysis or for younger patients who do not want to have to visit hospital three times a week.
- The majority of patients do Continuous Ambulatory Peritoneal Dialysis (CAPD), which involves four 2-litre exchanges/day

Complications:

1) Peritonitis:

- ⇒ Coagulase-negative staphylococci such as *Staphylococcus epidermidis* the most common cause.
- ⇒ *Staphylococcus aureus* is another common cause

2) sclerosing peritonitis

PD peritonitis

- PD peritonitis is an emergency and requires prompt broad spectrum antibiotic therapy.
- Antibiotics delivered through the intra-peritoneal route are preferred to intravenous route
- Whilst antibiotic policies differ among hospitals, initial antibiotic regimes should cover Gram positive (including MRSA) and Gram negative organisms.
- Although laboratory tests are helpful, antibiotic therapy should not be delayed for the results of these tests (CBC, CRP, C/SS).

Renal vascular disease

- Renal vascular disease is most commonly due to **atherosclerosis** (> 95% of patients).
- It is associated with risk factors such as smoking and HTN that cause atheroma elsewhere in the body.
- It may present as HTN, CKD or 'flash' pulmonary oedema.
- In younger patients however **fibromuscular dysplasia** (FMD) needs to be considered.
- FMD is more common in young women and characteristically has a 'string of beads' appearance on angiography.
- Patients respond well to balloon angioplasty ?????

Investigation

- **MR angiography** is now **the investigation of choice**
- CT angiography
- conventional renal angiography is less commonly performed used nowadays, but may still have a role when planning surgery

Renal artery stenosis (RAS)

- The current evidence favours medical therapy in these patients, that is, an antiplatelet agent (aspirin), lipid lowering therapy (simvastatin) and tight blood pressure control (amlodipine).
- RAS is often unmasked when patients commence an ACE inhibitor, as these drugs reduce vasoconstriction in the efferent arterioles, which in turn reduces glomerular filtration pressure. In patients with critical RAS this can often prompt a precipitous drop in glomerular filtration rate.
- The recently reported ASTRAL trial was a randomised controlled trial (RCT) comparing medical and interventional (renal artery angioplasty and stenting) approaches to treating RAS.
- It found that revascularisation carried significant risks and conferred no significant clinical benefit.
- There is some controversy over the trial recruitment strategy as it only included patients with established RAS where the responsible clinician was "unsure if revascularisation would be beneficial", but for now current practice is to avoid routine referral for intervention in newly diagnosed RAS.
- It is most important to control his blood pressure, but with an alternative to ACE inhibition in the first instance. Cautious, low dose ACE inhibition is sometimes an option in these patients when other agents have failed to reduce the blood pressure, but this should only occur under close supervision.

- ❌ Renal artery stenosis is a potential cause of hypertension.
- ❌ Typically patients are vasculopaths and poor prognosis (80% mortality at five years) is related to concurrent coronary disease.
- ❌ It is almost exclusively caused by atherosclerosis, but other causes include fibromuscular dysplasia, vasculitis and external compression.
- ❌ Typical ultrasound changes are asymmetrical kidneys; the affected kidney >2 cm smaller than the unaffected kidney.
- ❌ ACE inhibitors are contraindicated in renal artery stenosis as they inhibit the contraction of the efferent arterioles which promote glomerular filtration in the disease.

Retroperitoneal fibrosis

Lower back pain is the most common presenting feature

Associations

- 1) Riedel's thyroiditis
- 2) previous radiotherapy
- 3) sarcoidosis
- 4) inflammatory abdominal aortic aneurysm
- 5) drugs: methysergide

Renal stones

Risk factors

- 1) dehydration
- 2) hyperparathyroidism, hypercalciuria, hypercalcaemia
- 3) cystinuria
- 4) high dietary oxalate
- 5) renal tubular acidosis
- 6) medullary sponge kidney, polycystic kidney disease
- 7) beryllium or cadmium exposure

Risk factors for urate stones

- 1) gout
- 2) ileostomy: loss of bicarbonate and fluid results in acidic urine, causing the precipitation of uric acid

Drug causes

- 1) drugs that promote calcium stones: steroids, loop diuretics, acetazolamide, theophylline
- 2) thiazides can prevent calcium stones (increase distal tubular calcium resorption)

Imaging

The table below summarises the appearance of different types of renal stone on x-ray

Type	Frequency	Radiograph appearance
Calcium oxalate	40%	Opaque
Mixed calcium oxalate/phosphate stones	25%	Opaque
Calcium phosphate	10%	Opaque
Triple phosphate stones*	10%	Opaque
Urate stones	5-10%	Radio-lucent
Cystine stones	1%	Semi-opaque, 'ground-glass' appearance
Xanthine stones	<1%	Radio-lucent

Stag-horn calculi

- Involve the renal pelvis and extend into at least 2 calyces.
- They develop in alkaline urine and are composed of struvite (ammonium magnesium phosphate, triple phosphate).
- **Ureaplasma urealyticum** and **Proteus** infections predispose to their formation (Urease producing bacteria)

Renal stones management:

Acute management of renal colic

Medication:

- the British Association of Urological Surgeons (BAUS) recommend **diclofenac** (intramuscular/oral) as the analgesia of choice for renal colic*
- BAUS also endorse the widespread use of **alpha-adrenergic blockers** to aid ureteric stone passage

*Diclofenac use is now less common following the MHRA warnings about cardiovascular risk.

It is therefore likely the guidelines will change soon to an alternative NSAID such as naproxen

Imaging:

- patients presenting to the Emergency Department usually have a KUB x-ray (shows 60% of stones)
- The imaging of choice is a **non-contrast CT** (NCCT). 99% of stones are identifiable on NCCT. Many GPs now have direct access to NCCT
 - ⇒ Stones < 5 mm will usually pass spontaneously.
 - ⇒ Lithotripsy and nephrolithotomy may be for severe cases.

Prevention of renal stones

A) **Calcium stones** may be due to hypercalciuria, which is found in up to 5-10% of the general population.

- 1) high fluid intake
- 2) low animal protein,
- 3) low salt diet (a low calcium diet has not been shown to be superior to a normocalcaemic diet)
- 4) thiazides diuretics (increase distal tubular calcium resorption)

B) **Oxalate stones:**

TTT:

- **cholestyramine** reduces urinary oxalate secretion
- **pyridoxine** reduces urinary oxalate secretion

☒ Oxalate stones are uncommon in dietary excess of oxalate.

☒ However enteric oxaluria may occur in a number of disorders in which malabsorption results in excessive colonic absorption of oxalate. These include:

- 1) Coeliac disease
- 2) Crohn's disease
- 3) Chronic pancreatitis, and
- 4) Short bowel syndrome.

High fluid intake and **calcium carbonate** are mainstay of **prevention**.

C) **Uric acid stones**

- allopurinol
- urinary alkalinization e.g. oral bicarbonate

Some notes from onexamination;

Oxalate stone

- Hyperoxaluria occurs both in patients with an ileal resection and in patients with a short bowel who have had a distal small bowel resection (for example, Crohn's disease, infarcted bowel).
- It is caused by increased absorption of oxalate by the colon.
- Bile salts in the colon increase oxalate absorption.
- Hyperoxaluria is associated with renal stone formation and the propensity to form stones is reduced when oxalate intake is reduced.

Management:

- Treatment involves:
 - ⇒ Having a low-oxalate diet and taking cholestyramine to bind bile salts and citrate to prevent stone formation.
 - ⇒ Low-oxalate diets typically exclude cocoa, peanut products, tea, coffee, wheat germ, rhubarb, beetroot, spinach, tofu and soybeans and restrict certain citrus drinks (lemon juice is a natural source of citrate and its consumption by oxalate stone formers can reduce stone formation/growth), diet soda drinks, tomatoes and fruit.
 - ⇒ In addition, calcium excretion can be reduced by using bendofluazide 5 mg daily and regular pyridoxine 10 mg daily can reduce hyperoxaluria.
- ☒ **Calcium phosphate stones** can be prevented with **thiazide diuretics** and a **low calcium diet** (restrict dairy products).
- ☒ **Triple phosphate stones** often cause staghorn calculi and patients require prophylactic antibiotics to prevent recurrent infections; these stones may require surgery for removal.
- ☒ **Urate stones** may be prevented by giving regular allopurinol and by urinary alkalinisation.
- ☒ Methods of preventing **cysteine stones** include **adequate hydration** (increase daily fluid intake), **low methionine diet**, **D-penicillamine** and **urinary alkalinisation**.

This gentleman has had a calcium urinary tract stone. He has normal serum calcium, but raised urinary excretion of calcium.

Idiopathic hypercalciuria is often familial, the most common cause being increased gastrointestinal absorption of calcium. The most common stones are calcium oxalate stones.

He should aim for a daily urinary output in excess of 2000 ml.

A high protein intake is associated with urinary stones, and by reducing his dairy dietary intake he may reduce his gastrointestinal absorption of calcium, but the main initial treatment is to increase his urine volume.

- Potassium citrate and potassium bicarbonate can be used to alkalinise the urine, to prevent the formation of cystine containing stones. Potassium citrate also chelates calcium and is useful in combination with thiazides in those who develop hypokalaemia on diuretics.
- Thiazide diuretics reduce renal tubular calcium excretion, and therefore can prevent calcium stone formation.
- Loop diuretics increase urinary excretion of calcium, and therefore would exacerbate calcium renal stone formation.

Renal stones

Type of stones	Features	Percentage of all calculi
Calcium oxalate	• Hypercalciuria is a major risk factor (various causes) • Hyperoxaluria may also increase risk • Hypocitraturia increases risk because citrate forms complexes with calcium making it more soluble • Hyperuricosuria may cause uric acid stones to which calcium oxalate binds Stones are radio-opaque (less than calcium phosphate stones)	85%
Cystine	• Inherited recessive disorder of transmembrane cystine transport leading to decreased absorption of cystine from intestine and renal tubule • Multiple stones may form • Relatively radiodense because they contain sulphur	1%
Uric acid	• Uric acid is a product of purine metabolism • May precipitate when urinary pH low • May be caused by diseases with extensive tissue breakdown e.g. malignancy • More common in children with inborn errors of metabolism • Radiolucent	5-10%
Calcium phosphate	• May occur in RTA, high urinary pH increases supersaturation of urine with calcium and phosphate • RTA types 1 and 3 increase risk of stone formation (types 2 and 4 do not) • Radio-opaque stones (composition similar to bone)	10%
Struvite	• Stones formed from magnesium, ammonium and phosphate • Occur as a result of urease producing bacteria (and are thus associated with chronic infections) • Under the alkaline conditions produced, the crystals can precipitate • Slightly radio-opaque	2-20%

Effect of urinary pH on stone formation

- Urine pH will show individual variation (from pH 5-7).
- Post prandially the pH falls as purine metabolism will produce uric acid.
- Then the urine becomes more alkaline (alkaline tide).
- When the stone is not available for analysis the pH of urine may help to determine which stone was present.

Stone type	Urine acidity	Mean urine pH
Calcium phosphate	Normal- alkaline	>5.5
Calcium oxalate	Variable	6
Uric acid	Acid	5.5
Struvate	Alkaline	>7.2
Cystine	Normal	6.5

Causes of Sterile pyuria:

- 1) partially treated UTI
- 2) urethritis e.g. *Chlamydia*
- 3) renal tuberculosis
- 4) renal stones
- 5) appendicitis
- 6) bladder/renal cell cancer
- 7) adult polycystic kidney disease
- 8) analgesic nephropathy

Renal cell cancer

- Renal cell cancer is also known as hypernephroma
- Accounts for 85% of primary renal neoplasms.
- It arises from proximal renal tubular epithelium

Associations:

- 1) more common in middle-aged men
- 2) smoking
- 3) von Hippel-Lindau syndrome
- 4) tuberous sclerosis

*incidence of renal cell cancer is only slightly increased in patients with ADPKD

Features:

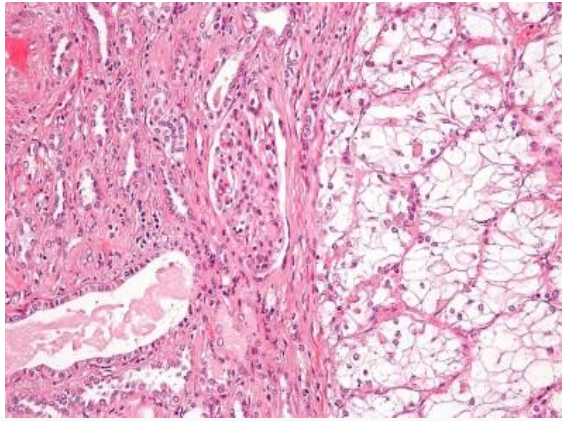
- 1) classical triad: haematuria, loin pain, abdominal mass
- 2) pyrexia of unknown origin FUO
- 3) left varicocele (due to occlusion of left testicular vein)
- 4) endocrine effects:
 - ⇒ may secrete erythropoietin (polycythaemia),
 - ⇒ renin,
 - ⇒ PTH (hypercalcaemia),
 - ⇒ ACTH
- 5) 25% have metastases at presentation

Management:

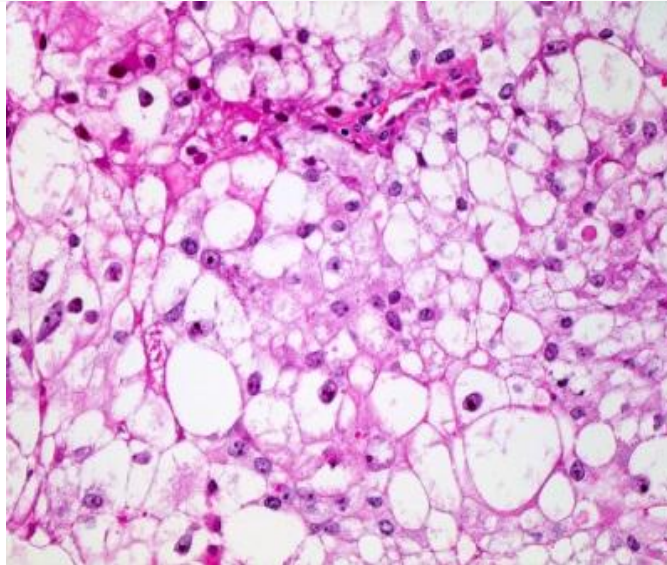
- 1) for confined disease a **partial or total nephrectomy** depending on the tumour size
- 2) **alpha-interferon** and **interleukin-2** have been used to reduce tumour size and also treat patients with metastases
- 3) **receptor tyrosine kinase inhibitors** (e.g. **sorafenib**, **sunitinib**) have been shown to have superior efficacy compared to interferon-alpha



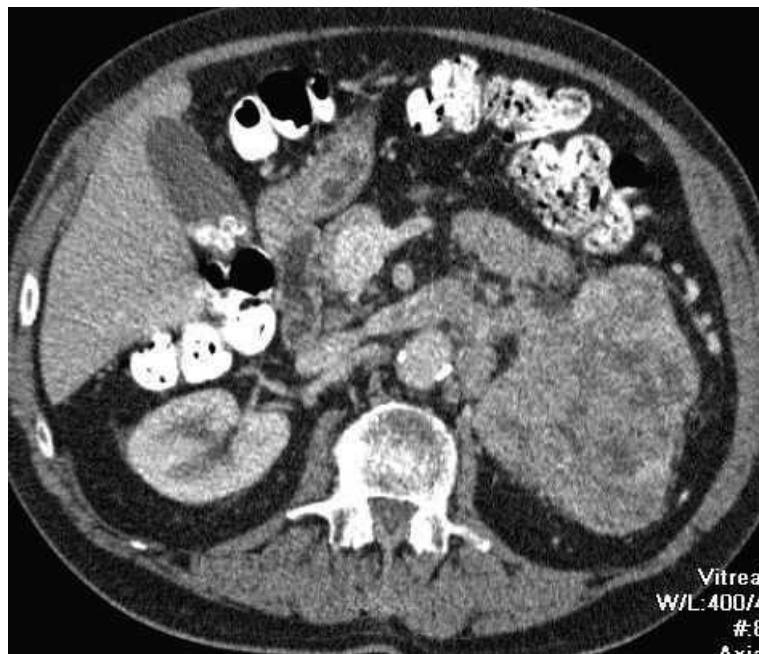
Coronal CT scan of a middle-aged woman with renal cell cancer. Note the heterogeneously enhancing mass at the upper pole of the right kidney



Left: normal kidney. Right: 'clear-cell' pattern of renal cell carcinoma



'Clear-cell' pattern of renal cell carcinoma - clear cytoplasm, small nuclei



This CT demonstrates a huge left sided renal mass that is extending into the renal vein/IVC and is most likely a renal cell carcinoma.

Wilms' tumour

- Wilms' nephroblastoma is one of the most common **childhood malignancies**.
- It typically presents in children under 5 years of age, with a median age of 3 years old

Features:

- abdominal mass (most common presenting feature)
- painless haematuria
- flank pain
- other features: anorexia, fever
- unilateral in 95% of cases
- metastases are found in 20% of patients (most commonly lung)

Associations:

- 1) Hemihypertrophy
- 2) **Beckwith-Wiedemann syndrome**: an inherited condition associated with organomegaly, macroglossia, abdominal wall defects, Wilm's tumour and neonatal hypoglycaemia.
- 3) **As part of WAGR syndrome** with Aniridia, Genitourinary malformations, mental Retardation, also WT1 gene deletion.
- 4) one-third of cases are associated with a mutation in the WT1 gene on chromosome 11

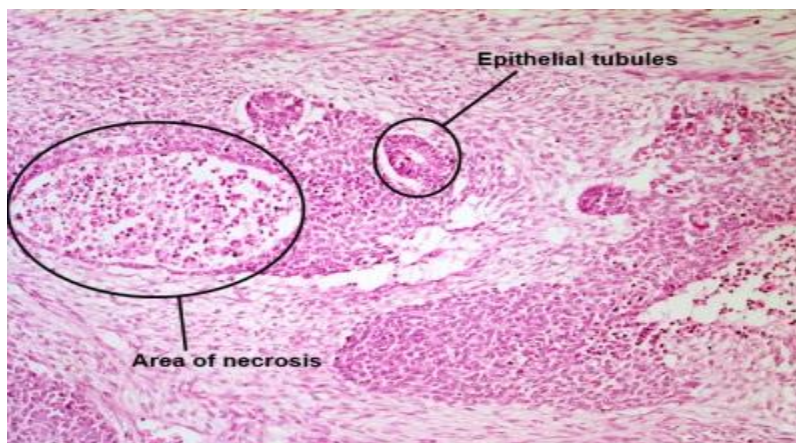
Aniridia (absence of the iris)

The G is sometimes instead given as "gonadoblastoma," since the genitourinary anomalies are tumours of the gonads (testes or ovaries).

(A subset of WAGR syndrome patients shows severe **childhood obesity**; the acronym WAGRO (O for **OBESENITY**) used to describe this category)

Management:

- nephrectomy
- chemotherapy
- radiotherapy if advanced disease
- prognosis: good, 80% cure rate



Histological features include epithelial tubules, areas of necrosis, immature glomerular structures, stroma with spindle cells and small cell blastomatous tissues resembling the metanephric blastema

Renal transplant

HLA typing and graft failure

- The human leucocyte antigen (HLA) system is the name given to the major histocompatibility complex (MHC) in humans.
- It is coded for on chromosome 6.
- Some basic points on the HLA system:
 - ☒ Class 1 antigens include A, B and C.
 - ☒ Class 2 antigens include DP, DQ and DR
 - ☒ when HLA matching for a renal transplant the relative importance of the HLA antigens are as follows DR > B > A

Graft survival

- 1 year = 90%, 10 years = 60% for cadaveric transplants
- 1 year = 95%, 10 years = 70% for living-donor transplants

Post-op problems

- ATN of graft
- vascular thrombosis
- urine leakage
- UTI

Hyperacute acute rejection (minutes to hours)

- due to pre-existent antibodies against donor HLA type 1 antigens (type II hypersensitivity reaction)
- rarely seen due to HLA matching

Acute graft failure (< 6 months)

- Usually due to mismatched HLA. Cell-mediated (cytotoxic T cells)
- may be reversible with steroids and immunosuppressants
- other causes include CMV

Causes of chronic graft failure (> 6 months)

- both antibody and cell mediated mechanisms cause fibrosis to the graft (CAN)
- recurrence of original renal disease (MCGN > IgA > FSGS)

Acute cellular rejection:

- Approximately 25% of transplant patients will have at least one episode of rejection mostly between days seven and 21, and less commonly up to three months post-operation.
- It is often clinically silent, with only a sharp rise in serum creatinine pointing towards the diagnosis.
- Doppler ultrasound studies may show a sharp deterioration in graft perfusion, and kidney biopsy will show invading lymphocytes penetrating the tubular basement membrane, causing tubulitis.
- Treatment is with IV bolus of high dose steroids.
- Long term graft function will be compromised if the rejection episode is not completely reversed.
- CMV infection has been associated with increased graft rejection and renal artery stenosis in renal transplant recipients.
- Cyclosporine is a calcineurin inhibitor which is a potent immunosuppressant and nephrotoxin.
- Cyclosporine can cause a dose dependent increase in urea and creatinine in the first few weeks of taking, and also long term graft failure. This is probably related to the total amount of ciclosporin taken. In the question they will mention that the dose has recently been increased
- Pyelonephritis of the transplanted kidney is a particular problem in the early immunosuppressed period.
- Pyelonephritis would present with low grade pyrexia, tender, swollen kidney and deteriorating graft function.

Kidney transplant recipients have a high risk of developing non-melanoma skin cancer. Cancer surveillance is an important consideration in kidney transplant recipients.

Fluid therapy

- The prescription of intravenous fluids is one of the most common tasks that junior doctors need to do.
- **The typical daily requirement is:**
 - **1.5 ml/kg/hr fluid** - for a 80kg man around 2-3 liters/day
 - **40-70 mmol potassium**
 - **70-150 mmol sodium**
- **This is why the typical regime prescribed for patients is:**
 - **1 litre 5% dextrose with 20mmol potassium over 8 hours**
 - **1 litre 0.9% normal saline with 20mmol potassium over 8 hours**
 - **1 litre 5% dextrose with 20mmol potassium over 8 hours**
- The amount of fluid patients require obviously varies according to their recent and past medical history. For example a patient who is post-op and is having significant losses from drains will require more fluid whereas a patient with heart failure should be given less fluid to avoid precipitating pulmonary oedema.

The table below shows the electrolyte concentrations (in millimoles/litre) of plasma and the most commonly used fluids:

	Na ⁺	Cl ⁻	K ⁺	HCO ₃ ⁻	Ca ²⁺
Plasma	135-145	98-105	3.5-5	22-28	2.3-2.6
0.9% normal saline	150	150	-	-	-
5% dextrose	-	-	-	-	-
Hartmann's solution	131	111	5	29	2

Hyponatraemia

- Hyponatraemia may be caused by water excess or sodium depletion.

Causes of pseudohyponatraemia include

- 1) Hyperlipidaemia (increase in serum volume) or a
- 2) taking blood from a drip arm.

- Urinary sodium and osmolality levels aid making a diagnosis:

Urinary sodium > 20 mmol/l:

+ Sodium depletion, renal loss (**patient often hypovolaemic**)

- 1) diuretics
- 2) Addison's
- 3) diuretic stage of renal failure

+ Patient often euvolaemic:

- 1) SIADH (urine osmolality > 500 mmol/kg)
- 2) Hypothyroidism

Urinary sodium < 20 mmol/l:

+ Sodium depletion, extra-renal loss

- 1) diarrhoea, vomiting, sweating
- 2) burns, adenoma of rectum

Water excess: (Patient often **hypervolaemic** and **oedematous**)

- 1) secondary hyperaldosteronism: heart failure, cirrhosis
- 2) reduced GFR: renal failure
- 3) IV dextrose,
- 4) psychogenic polydipsia

Hyponatraemia: correction

Central pontine myelinolysis

- demyelination syndrome caused by rapid correction of chronic hyponatraemia
- may lead to quadriplegia and bulbar palsy
- diagnosis: MRI brain

Hypernatraemia

Causes

- 1) dehydration
- 2) osmotic diuresis e.g. HONK coma
- 3) DI
- 4) excess IV saline

Cerebral oedema:

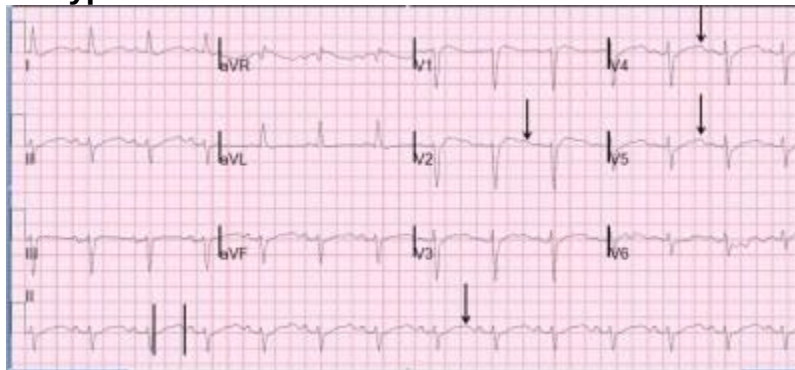
- Hypernatraemia should be corrected with great caution. Although brain tissue can lose sodium and potassium rapidly, lowering of other osmolytes (and importantly water) occurs at a slower rate, predisposing to cerebral oedema
- Resulting in seizures, coma and death.
- It is generally accepted that a rate of no greater than 0.5 mmol/hour correction is appropriate.

Hypokalaemia

ECG features of hypokalaemia

- U waves
- small or absent T waves (occasionally inversion)
- prolong PR interval
- ST depression
- long QT

The ECG below shows typical U waves. Note also the borderline PR interval



One registered user suggests the following rhyme

- In Hypokalaemia, U have no Pot and no T, but a long PR and a long QT

ECG changes seen in hyperkalaemia include tall-tented T waves, small P waves, widened QRS leading to a sinusoidal pattern and asystole.

Hyperkalaemia

- Plasma potassium levels are regulated by a number of factors including aldosterone, acid-base balance and insulin levels.
- Metabolic acidosis is associated with hyperkalaemia as H^+ and K^+ ions compete with each other for exchange with Na^+ ions across cell membranes and in the distal tubule.
- Untreated hyperkalaemia may cause life-threatening arrhythmias.
- Precipitating factors should be addressed (e.g. acute renal failure) and aggravating drugs stopped (e.g. ACE inhibitors).
- ECG changes seen in hyperkalaemia include tall-tented T waves, small P waves, widened QRS leading to a sinusoidal pattern and asystole.

Causes of hyperkalaemia:

- acute renal failure
- drugs*: potassium sparing diuretics, ACE inhibitors, angiotensin 2 receptor blockers, spironolactone, cyclosporine, heparin**
- metabolic acidosis
- Addison's
- rhabdomyolysis
- massive blood transfusion

Foods that are high in potassium:

- salt substitutes (i.e. Contain potassium rather than sodium)
- bananas, oranges, kiwi fruit, avocado, spinach, tomatoes

*beta-blockers interfere with potassium transport into cells and can potentially cause hyperkalaemia in renal failure patients - remember beta-agonists, e.g. Salbutamol, are sometimes used as emergency treatment

**both unfractionated and LMWH can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion

Management:

Management may be categorized by the aims of treatment

- **Stabilization of the cardiac membrane**
 - intravenous calcium gluconate
- **Short-term shift in potassium from ECF to ICF compartment**
 - combined insulin/dextrose infusion
 - nebulised salbutamol
- **Removal of potassium from the body**
 - calcium resonium (orally or enema)
 - loop diuretics
 - dialysis

The initiation of emergency renal replacement therapy is usually required for:

- 1) Acute life threatening hyperkalaemia which is resistant to treatment
- 2) Development of metabolic acidosis which is non-responsive to fluid.
- 3) Development of fluid overload, which may manifest itself as pulmonary oedema.
- 4) Development of uraemia which may manifest itself as pericarditis, neuropathy and confusional state.

Hypomagnesaemia

Causes:

- Diuretics, gittelman syndrome
- total parenteral nutrition TPN
- diarrhoea
- alcohol
- hypokalaemia, hypocalcaemia

Features: **similar to hypocalcaemia**

- paraesthesia
- tetany
- seizures
- arrhythmias
- decreased PTH secretion → hypocalcaemia
- exacerbates digoxin toxicity
- ECG features similar to those of hypokalaemia

Hypermagnesaemia الماغنسيوم يرخى كل حاجة

- Nausea, Drowsiness
- Double vision
- Vasodilatation, and
- Hypotension (myocardial depression + vasodilatation).
- Bradycardia
- Respiratory depression
- Loss of deep tendon reflexes
- Coma, and
- Cardiac arrest.

Hypophosphataemia

Causes:

- 1) alcohol excess
- 2) acute liver failure
- 3) DKA
- 4) refeeding syndrome
- 5) primary hyperparathyroidism
- 6) osteomalacia

Consequences:

- haemolysis
- WBC and platelet dysfunction
- muscle weakness and rhabdomyolysis
- CNS dysfunction

Acid Base Balance

- ✗ The anion gap is a simple method for discerning causes of metabolic acidosis.
- ✗ It relies on the fact that the concentration of cations in plasma must equal the concentration of anions.
- ✗ Cations have positive charge, anions have negative charge.

$$[\text{Cations}] = [\text{Anions}]$$

- ✗ Most ions are unmeasured and individually have a low concentration.
- ✗ The measured ions in sufficient concentration are sodium, potassium, chloride and bicarbonate. Therefore:

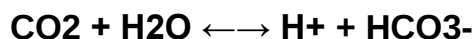
$$[\text{Na}] + [\text{K}] + [\text{unmeasured cations}] = [\text{Cl}] + [\text{HCO}_3] + [\text{unmeasured anions}]$$

And rearranging:

$$([\text{Na}] + [\text{K}]) - ([\text{Cl}] + [\text{HCO}_3]) = [\text{unmeasured anions}] - [\text{unmeasured cations}].$$

- ✗ **The anion gap** is the difference between unmeasured anions and unmeasured cations
- ✗ In health is between 10-18 mmol/l.
- ✗ This value is helpful in discerning causes of metabolic acidosis,
 - ⇒ As if it is raised the acidosis is due to an unmeasured ion - such as lactate, ketones, salicylate in lactic acidosis, diabetic ketoacidosis and aspirin overdose respectively, and methanol or ethylene glycol poisoning
 - ⇒ A normal anion gap suggests an acidosis due to bicarbonate or chloride handling - such as renal tubular acidosis, diarrhoea, pancreatic fistula, ammonium chloride ingestion or acetazolamide.
- ✗ A metabolic alkalosis may be seen in vomiting, from other diuretics or excessive bicarbonate or antacid therapy.
- ✗ Respiratory acidosis is defined by a raised pCO₂ and is typically related to type 2 respiratory failure. It is seen in severe COPD, asthma, pneumonia or pulmonary oedema and hypoventilation due to sedatives, muscular disease (for example, myasthenia gravis) or chest wall trauma.
- ✗ Respiratory alkalosis is seen in any cause of hyperventilation, either due to anxiety, or in hypoxic states such as asthma where adequate ventilation is preserved.

- Carbonic anhydrase catalyses the first part of the reversible reaction in which carbon dioxide and water are converted to carbonic acid (and vice versa):



- In the kidney, carbonic anhydrase is found in the proximal convoluted tubule.
 - The equation is normally shifted to the left allowing the formed carbon dioxide to diffuse back into the systemic circulation.
 - In the presence of a carbonic anhydrase inhibitor, such as **acetazolamide**, the equation is shifted to the right and more H^+ and HCO_3^- is produced.
 - The H^+ is reabsorbed alongside chloride ions. However, the bicarbonate is passed in the urine as it is not easily absorbed in the nephron.
 - This results in a **hyperchloraemic, normal anion gap metabolic acidosis**.
- ☒ This effect can be used therapeutically to prevent acute mountain sickness. Whereas normally the hypoxic high altitude would stimulate ventilation resulting in a respiratory alkalosis, acetazolamide use causes net renal excretion of bicarbonate, correcting this abnormality.
- ☒ With respiratory alkalosis the kidneys would physiologically excrete bicarbonate, but this takes two to three days. Acetazolamide speeds this process.

Causes of respiratory alkalosis:

- Central causes - stroke, meningitis, CNS tumour
- Drugs - salicylates
- Anxiety
- Pregnancy.

Causes of metabolic alkalosis:

- Vomiting - anorexia nervosa, gastric outlet obstruction
- Ingestion of base
- Prolonged hypokalaemia of any cause - the kidney allows H^+ to be lost in an effort to retain K^+ . Diuretic therapy is a common example.
- Burns.

Renal tubular acidosis

All three types of renal tubular acidosis (RTA) are associated with **hyperchloraemic** metabolic acidosis (normal anion gap)

Type 1 RTA (distal)

- inability to generate acid urine (secrete H⁺) in distal tubule
- causes hypokalaemia
- complications include nephrocalcinosis and renal stones
- causes include idiopathic, RA, SLE, Sjogren's



Abdominal x-ray showing nephrocalcinosis - a classical finding in type 1 RTA

Type 2 RTA (proximal)

- decreased HCO₃⁻ reabsorption in proximal tubule
- causes hypokalaemia
- complications include osteomalacia

Causes include:

- 1) idiopathic,
- 2) as part of Fanconi syndrome,
- 3) Wilson's disease,
- 4) cystinosis,
- 5) outdated tetracyclines

Type 4 RTA (hyperkalaemic) **hyporeninemic hypoaldosteronemic**

- reduction in aldosterone leads in turn to a reduction in proximal tubular ammonium excretion
- causes hyperkalaemia
- causes include hypoaldosteronism, diabetes

Fanconi syndrome

Fanconi syndrome describes a generalised disorder of renal tubular transport resulting in:

- type 2 (proximal) renal tubular acidosis
- aminoaciduria
- glycosuria
- phosphaturia
- osteomalacia

Causes:

- cystinosis (most common cause in children)
- Sjogren's syndrome
- Wilson's disease
- multiple myeloma
- nephrotic syndrome

The following notes are some comments on important questions from on examination

Goodpasture's disease

- An auto-immune pulmonary renal syndrome due to circulating antibody to the glomerular basement membrane.
- In the acute setting, treatment is focused on managing life threatening complications of renal failure, such as hyperkalaemia, and removing the circulating auto-antibody responsible for disease.
- As this patient is receiving haemodialysis, the most important treatment in acute setting is plasmapheresis (therapeutic plasma exchange), as this will remove the circulating antibody.
- There is no role for intravenous immunoglobulins in the management of this disease.

Hypertensive emergency

- Recommendations from a clinical review target a reduction in blood pressure of around 25% during the first 24-48 hours
- The concern is that if blood pressure reduction is targeted more aggressively, disordered autoregulation may result in significant end organ damage.
- IV therapy with either sodium nitroprusside or labetalol is the initial therapy of choice.
- Alternatives include phentolamine or hydralazine.

Renal vein thrombosis:

- **Renal vein thrombosis** is often clinically silent.
- Association with hypercoagulable state, peripheral leg edema and flank pain in a patient presenting with AKI are all pertinent clues.
- Patients with renal vein thrombosis usually report rapidly worsening peripheral leg edema, and may report dull loin pain from the affected kidney.

- **Angiotensin-converting enzyme (ACE) inhibitors** can cause acute deterioration in renal function, mainly in patients with bilateral renovascular disease, and commonly within the first two weeks of treatment.
 - ACE inhibitors may also increase the serum potassium, through impairment of the angiotensin II mediated secretion of aldosterone. The higher the serum creatinine concentration, the greater the risk of hyperkalaemia.
 - Uncommonly, ACE inhibitors may cause progressive renal impairment in patients without renovascular disease, especially the elderly, which may be caused by a membranous glomerulonephritis.
-
- **Bendroflumethiazide**, a thiazide diuretic, inhibits sodium and chloride reabsorption in the distal convoluted tubule, resulting in increased sodium and free water clearance.
 - A secondary effect is the loss of potassium by increased secretion in the distal tubule in response to the increased intraluminal sodium. Therefore, bendroflumethiazide may cause hypokalaemia.
-
- **Triamterene**, a potassium sparing diuretic similar to amiloride, is occasionally prescribed with thiazide or loop diuretics, to prevent hypokalaemia.
 - It inhibits the movement of sodium through channels towards the end of the distal tubule and collecting ducts, preventing the passage of sodium from the urinary space into the tubular cells. This action causes hyperpolarisation of the apical plasma membrane, preventing the secretion of potassium into the collecting ducts.
 - Hyperkalaemia is common (>5%), and is unaffected by concurrent potassium depleting diuretics.
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- **Bartter's syndrome** is a rare, autosomal recessive disorder, caused by one of three mutations of the ion transporter or ion channel present in the thick ascending limb of the distal nephron.
 - Type I and II mutations present in infancy (often following premature birth and polyhydramnios) with severe dehydration, hypokalaemic alkalosis, hypercalciuria and nephrocalcinosis. Mortality is high.
 - Type III mutations present with a more varied clinical picture to type I and II, ranging in severity from near fatal volume depletion with hypokalaemic alkalosis and respiratory arrest, to mild disease presenting in teenagers with weakness and polyuria.
 - Nephrocalcinosis has not been described in type III mutations, therefore it can differentiate between type I and II disease, and type III disease.
 - Management is with long term potassium supplementation and care to avoid dehydration. The long term prognosis is uncertain.

The clinical presentation in rheumatoid includes

- Nail fold infarcts
- A leucocytoclastic vasculitis
- A peripheral neuropathy
- Pericarditis
- Gastrointestinal infarcts and
- Renal vasculitis.

Renal abnormalities are found in 25% of patients with rheumatoid vasculitis, usually presenting with proteinuria, microscopic haematuria and renal impairment.

Bartter's syndrome usually presents in childhood with severe muscle weakness. It is a salt wasting state, which is due to a defect in the loop of Henle chloride reabsorption (at the $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ cotransporter). Patients have low blood pressure and **severe hyperreninaemia**.

Conn's syndrome is caused by an adrenal adenoma secreting aldosterone. The clinical features include hypertension, hyperaldosteronism, hypokalaemia and **hyporeninaemia**.

Essential hypertension is not associated with endocrine or electrolyte abnormalities. In patients younger than 35 with hypertension, an endocrine cause should be excluded.

Fibromuscular dysplasia, a rare cause of hypertension and hypokalaemia is more common in women. It causes **hyperreninaemic hyperaldosteronism**.

Liquorice ingestion causes a primary aldosterone type picture. It is caused by glycyrrhizic acid contained in liquorice, blocking the enzyme 11 β hydroxysteroid dehydrogenase. This prevents the inactivation of cortisol, which in turn activates mineralocorticoid receptors in the kidney.

Renal biopsy:

- For a routine biopsy there is no preferable side to biopsy.
- Coagulation studies should always be performed prior to renal biopsy due to the risk of bleeding.
- Macroscopic haematuria can occur in up to 10% of renal biopsies.
- The hila of the kidneys lie at the L1 and L2 vertebral levels.
- Nephrectomy is a rare but serious complication of renal biopsy required to control bleeding. It should be consented for.

Extended spectrum beta lactamase (ESBL)

- This patient has an ESBL urine infection and is symptomatic.
- Meropenem has a broad spectrum of activity and is the right initial course of antibiotics in this case pending full sensitivities of the cultured organism.
- ESBL infections are becoming a greater problem in hospitals. These organisms have broader beta lactamases; enzymes capable of breaking down a larger variety of antibiotics.
- In this patient, the presence of renal cysts, a reservoir of infection and previous antibiotic use are likely to have led to this resistant strain.
- A broad spectrum antibiotic is required and of the list available, meropenem is the most suitable choice.
- Intravenous co-amoxiclav is unlikely to be adequate. Neither would erythromycin have the appropriate coverage.

- **In acute gout** with renal impairment, a trial of colchicine is the best option
- Colchicine is safe to use in renal impairment. It is generally advised to be taken to the point of onset of diarrheal symptoms, when its use should be discontinued. So long as the patient is adherent with the advise, renal function should not deteriorate
- The first line treatment for acute gout is a non-steroidal anti-inflammatory drug (NSAID) or colchicine. Given this patient's renal impairment, a NSAID would be contraindicated.
- Paracetamol will offer some mild pain relief but will not treat gout and so is not appropriate.
- Allopurinol should not be started in an acute attack of gout.
- Prednisolone is a reasonable choice but is usually tried as a second line treatment after NSAID use or colchicine.